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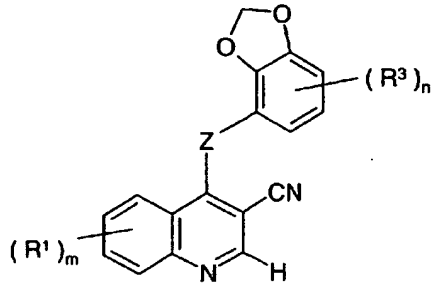

(I)

(57) Abstract: The invention concerns quinoline derivatives of Formula (I), wherein each of Z, m, R^1, n and R^3 have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

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QUINOLINE DERIVATIVES AS ANTITUMOUR AGENTS

The invention concerns a new use of quinoline derivatives, or pharmaceutically-acceptable salts thereof, which have been found to possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Cancer is a disease in which cells grow and divide in an uncontrolled fashion. This uncontrolled growth arises from abnormalities in signal transduction pathways that are used by normal cells to regulate cell growth and division in response to various signalling molecules. Normal cells do not proliferate unless stimulated to do so by specific signal molecules located outside the cell derived from nearby cells or tissues. Growth factors bind to the cell membrane via specific receptors which have intrinsic enzyme activity. These receptors relay the growth signal to the cell nucleus via a series of signalling proteins. In cancer, a number of defects in signal pathways are apparent. For example, cancer cells may produce their own growth factors which bind to their cognate receptors, resulting in an autocrine loop, or receptors may be mutated or overexpressed leading to an increased, continuous signal to proliferate. In addition, negative regulators of cell growth may be lost.

Oncogenes are cancer related genes which often encode abnormal versions of signal pathway components, such as receptor tyrosine kinases, serine-threonine kinases, or downstream signaling molecules such as the ras genes, which code for closely related small guanine nucleotide binding proteins which hydrolyse bound guanosine triphosphate (GTP) to guanosine diphosphate (GDP). Ras proteins are active in promoting cell growth and transformation when they are bound to GTP and inactive when they are bound to GDP. Transforming mutants of p21ras are defective in their GTPase activity and hence remain in the active GTP bound state. The ras oncogene is known to play an integral role in certain cancers, and has been found to contribute to the formation of over 20% of all cases of human cancer.

When activated by ligand, cell surface receptors which are coupled to the mitogenic response, such as growth factor receptors, initiate a chain of reactions which leads to the activation of guanine nucleotide exchange activity on ras. When in its active GTP-bound state, a number of proteins interact directly with ras at the plasma membrane resulting in signal transmission through several distinct pathways. The best characterised effector protein is the

product of the raf proto-oncogene. The interaction of raf and ras is a key regulatory step in the control of cell proliferation. Ras-mediated activation of the raf serine-threonine kinase in turn activates the dual-specificity MEK (MEK1 and MEK2), which is the immediate upstream activator of mitogen activated protein kinase (MAPKs known as extracellular signal regulated protein kinases or ERK1 and ERK2). To date, no substrates of MEK other than MAPK have been identified, though recent reports indicate that MEK may also be activated by other upstream signal proteins such as MEKK1 and Cot/Tpl-2. Activated MAPK translocates and accumulates in the nucleus, where it can phosphorylate and activate transcription factors such as Elk-1 and Sap1a, leading to the enhanced expression of genes such as that for c-fos.

The ras-dependent raf-MEK-MAPK cascade is one of the key signalling pathways responsible for transmitting and amplifying mitogenic signals from cell surface to the nucleus resulting in changes in gene expression and cell fate. This ubiquitous pathway appears essential for normal cell proliferation and constitutive activation of this pathway is sufficient to induce cellular transformation. Transforming mutants of p21ras are constitutively active, resulting in raf, MEK and MAPK activity and cell transformation. Inhibition of MEK activity using either antisense raf, a dominant negative MEK mutant or the selective inhibitor PD098059 have been shown to block the growth and morphological transformation of ras-transformed fibroblasts.

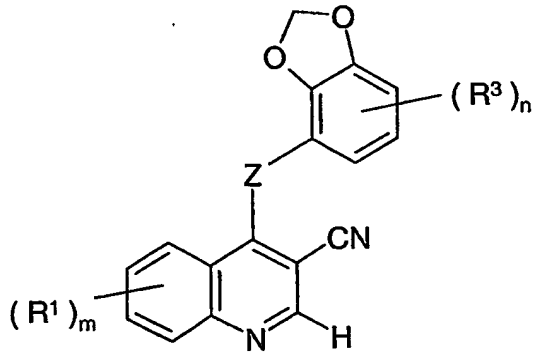
The mechanism of activation of raf, MEK and MAPK is through phosphorylation on specific serine, threonine or tyrosine residues. Activated raf and other kinases phosphorylate MEK1 on S218 and S222 and MEK2 on S222 and S226. This results in MEK activation and subsequent phosphorylation and activation of ERK1 on T190 and Y192 and ERK2 on T183 and Y185 by the dual specificity MEKs. Whilst MEK can be activated by a number of protein kinases, and active MAPKs phosphorylate and activate a number of substrate proteins including transcription factors and other protein kinases, MEKs appear specific and sole activators of MAPKs and could act as a focal point for cross-cascade regulation. MEK1 and MEK2 isoforms show unusual specificity and also contain a proline-rich insert between catalytic subdomains IX and X which is not present in any of the other known MEK family members. These differences between MEK and other protein kinases, together with the known role of MEK (MEK 1, MEK 2) and, more recently MEK 5, in proliferative signalling suggest that it may be possible to discover and employ selective MEK inhibitors as therapeutic agents for use in proliferative disease.

It is stated in International Patent Application WO 98/43960 that a range of 3-cyanoquinoline derivatives are useful in the treatment of cancer. Certain of the compounds are stated to be inhibitors of EGF receptor tyrosine kinase, others are stated to be inhibitors of the mitogen-activated protein kinase (MAPK) pathway and others are stated to be inhibitors of growth factors such as vascular endothelial growth factor (VEGF). There is no disclosure therein of any 2,3-methylenedioxyphenyl-containing 3-cyanoquinoline derivatives.

It is stated in International Patent Application WO 00/68201 that a range of 3-cyanoquinoline derivatives are also useful in the treatment of cancer. Certain of the compounds are stated to be inhibitors of MEK, a MAPK kinase. There is no disclosure therein of any 2,3-methylenedioxyphenyl-containing 3-cyanoquinoline derivatives.

It is stated in International Patent Application WO 00/18761 that a range of 3-cyanoquinoline derivatives are also useful in the treatment of cancer. Certain of the compounds are stated to be inhibitors of MEK. There is no disclosure therein of any 4-(2,3-methylenedioxyanilino)-3-cyanoquinolines.

According to one aspect of the invention there is provided the use of a quinoline derivative of the Formula I



I

wherein **Z** is an O, S, SO, SO_2, $N(R^2)$ or $C(R^2)_2$ group, wherein each R^2 group, which may be the same or different, is hydrogen or (1-6C)alkyl;

m is 0, 1, 2, 3 or 4;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,

N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_m$ is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-

(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

n is 0, 1, 2 or 3; and

$\mathbf{R^3}$ is halogeno, trifluoromethyl, cyano, nitro, formyl, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^6-R^{11}$$

wherein X^6 is a direct bond or is selected from O and $N(R^{12})$, wherein R^{12} is hydrogen or (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$$-X^7-Q^5$$

wherein X^7 is a direct bond or is selected from O, S, SO, SO_2, $N(R^{13})$, CO, $CH(OR^{13})$, $CON(R^{13})$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ and $N(R^{13})C(R^{13})_2$, wherein R^{13} is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q^5 optionally bears 1 or 2 oxo or thioxo substituents,

or a pharmaceutically-acceptable salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

According to a further feature of the invention there is provided a method for producing an anti-proliferative effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises

administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of MEK enzymes that are involved in the MAPK pathway. Particular enzymes that the tumours may be sensitive to are MEK 1, MEK 2 and MEK 5.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of MEK enzymes that are involved in the MAPK pathway which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a MEK enzyme inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a MEK enzyme inhibitory effect which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a novel quinoline derivative of Formula I, as hereinbefore defined, where Z, m and R^1 are as hereinbefore defined, n is 1, 2 or 3 and at least one R^3 is formyl, or a pharmaceutically-acceptable salt.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and also (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes

methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (Q^1 to Q^5) when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.

A suitable value for any one of the 'Q' groups (Q^1 or Q^3) when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for any one of the 'Q' groups (Q^1 or Q^3) when it is (3-7C)cycloalkenyl or for the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^5) when it is heteroaryl or for the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

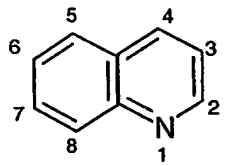
A suitable value for any one of the 'Q' groups (Q^1 to Q^5) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms

selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, tetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

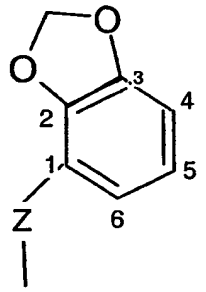
A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

In structural Formula I there is a hydrogen atom at the 2-position on the quinoline ring. It is to be understood thereby that the R^1 substituents may only be located at the 5-, 6-, 7- or 8-positions on the quinoline ring *i.e.* that the 2-position remains unsubstituted. It is further to be understood that the R^3 group that may be present on the 2,3-methylenedioxyphenyl group within structural Formula I may be located on the phenyl ring or on the methylene group within the 2,3-methylenedioxy group. Preferably, any R^3 group that is present on the 2,3-methylenedioxyphenyl group within structural Formula I is located on the phenyl ring thereof.

Throughout this patent application , the quinoline ring sysem will be numbered as indicated in the formula below



The 2,3-methylenedioxyphenyl group will be numbered as



Suitable values for any of the 'R' groups (R^1 to R^{13}) or for various groups within an R^1 or R^3 substituent include :-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-6C)alkenyloxy:	vinyloxy and allyloxy;
for (2-6C)alkynyloxy:	ethynyloxy and 2-propynyloxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
for (1-6C)alkylsulphinyl:	methylsulphinyl and ethylsulphinyl;
for (1-6C)alkylsulphonyl:	methylsulphonyl and ethylsulphonyl;
for (1-6C)alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;
for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for N-(1-6C)alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
for N,N-di-[(1-6C)alkyl]carbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
for (2-6C)alkanoyl:	acetyl and propionyl;
for (2-6C)alkanoyloxy:	acetoxy and propionyloxy;

for (2-6C)alkanoylamino: acetamido and propionamido;

for N-(1-6C)alkyl-(2-6C)alkanoylamino: N-methylacetamido and N-methylpropionamido;

for N-(1-6C)alkylsulphamoyl: N-methylsulphamoyl and N-ethylsulphamoyl;

for N,N-di-[(1-6C)alkyl]sulphamoyl: N,N-dimethylsulphamoyl;

for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;

for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and N-methylethanesulphonylamino;

for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;

for N-(1-6C)alkyl-(3-6C)alkenoylamino: N-methylacrylamido and N-methylcrotonamido;

for (3-6C)alkynoylamino: propiolamido;

for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;

for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;

for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;

for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;

for halogeno-(1-6C)alkyl: chloromethyl, 2-chloroethyl, 1-chloroethyl and 3-chloropropyl;

for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;

for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;

for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl; and

for (1-6C)alkoxycarbonylamino-(1-6C)alkyl:

methoxycarbonylaminomethyl,
ethoxycarbonylaminomethyl,
tert-butoxycarbonylaminomethyl and
2-methoxycarbonylaminoethyl.

A suitable value for $(R^1)_m$ when it is a (1-3C)alkylenedioxy group is, for example, methylenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions.

When, as defined hereinbefore, an R^1 group forms a group of the formula Q^1-X^1- and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^4)_2$ linking group which is attached to the quinoline ring and the oxygen atom is attached to the Q^1 group. Similarly, when, for example a CH_3 group within a R^1 substituent bears a group of the formula -X^3-Q^3 and, for example, X^3 is a $C(R^7)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^7)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^3 group. A similar convention applies to the attachment of the groups of the formulae Q^2-X^2- and -X^7-Q^5.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O, $CON(R^5)$ or C≡C. For example, insertion of a C≡C group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-ynyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent such as a group of the formula Q^2-X^2- wherein X^2 is, for example, NHCO and Q^2 is a heterocyclyl-(1-6C)alkyl group, suitable R^1 substituents so formed include, for example, N-[heterocyclyl-(1-6C)alkyl]carbamoylvinyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or N-[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl

substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH_2 group and there are suitably 1, 2 or 3 such substituents present on each said CH_3 group.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent as defined hereinbefore, suitable R^1 substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted heterocyclyl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, hydroxy-substituted amino-(2-6C)alkylamino groups such as 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy, (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as 2-methylsulphonylethoxy and heterocyclyl-substituted (1-6C)alkylamino-(1-6C)alkyl groups such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and 3-morpholinopropylaminomethyl.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I for use according to the invention is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl) amine.

Particular compounds of Formula 1 for use according to the invention include, for example, quinoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof,

wherein, unless otherwise stated, each of Z, m, R^1, n and R^3 has any of the meanings defined hereinbefore or in paragraphs (a) to (t) hereinafter :-

(a) Z is O, S, SO, SO_2, CH_2 or NH;

(b) Z is O;

(c) Z is NH;

(d) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino; (3-6C)alkynoylamino and N-(1-6C)alkyl-(3-6C)alkynoylamino, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ and $OC(R^4)_2$ wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl, or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is CO or $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno groups or a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

(2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(e) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, NH, CONH, NHCO and OCH_2 and Q^1 is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, tetrahydrofuran-3-yl, 3- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CONH, NHCO, CH=CH and C≡C,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of the formula :

$$Q^2\text{-}X^2\text{-}$$

wherein X^2 is a direct bond or is CO, NHCO or N(Me)CO and Q^2 is pyridyl, pyridylmethyl, 2-pyridylethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl,

piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^3 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and N,N-dimethylcarbamoyl,

or optionally bears 1 substituent selected from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and NH and R^8 is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl,

methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, NH and CO and Q^4 is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(f) m is 1 and the R^1 group is located at the 6- or 7-position or m is 2 and each R^1 group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R^1 is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy,

3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino, 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and when R^1 is a vinyl or ethynyl group, the R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl, or from a group of the formula :

$$Q^2\text{-}X^2\text{-}$$

wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^2 is imidazolylmethyl, 2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino,

N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and methoxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(g) m is 1 and the R^1 group is located at the 6- or 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, benzyloxy, 2-imidazol-1-ylethoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any phenyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(h) n is 0;

(i) n is 1 or 2 and the R^3 groups, which may be the same or different, are located at the 5- and/or 6-positions of the 2,3-methylenedioxyphenyl group and are selected from halogeno, trifluoromethyl, cyano, hydroxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy;

(j) n is 1 or 2 and the R^3 groups, which may be the same or different, are located at the 5- and/or 6-positions of the 2,3-methylenedioxyphenyl group and are selected from fluoro, chloro, bromo, iodo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, isopropenyl, ethynyl, 1-propynyl, 2-propynyl, methoxy and ethoxy;

(k) n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxyphenyl group, especially the 6-position, and is selected from chloro, bromo, trifluoromethyl, hydroxy, methyl, ethyl, methoxy and ethoxy;

(l) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino and N-(1-6C)alkyl-(3-6C)alkynoylamino, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ and $OC(R^4)_2$ wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl, or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^2\text{-}X^2\text{-}$$

wherein X^2 is a direct bond or is CO or $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno groups or a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$$\text{-}X^3\text{-}Q^3$$

wherein X^3 is a direct bond or is selected from O, $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl and (2-6C)alkanoyl, or optionally bears 1 substituent selected from a group of the formula :

$$\text{-}X^4\text{-}R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,

(2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(m) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, vinyl, allyl, but-3-enyl, pent-4-enyl, hex-5-enyl, ethynyl, 2-propynyl, but-3-ynyl, pent-4-ynyl, hex-5-ynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, allyloxy, but-3-enyloxy, pent-4-enyloxy, hex-5-enyloxy, ethynyloxy, 2-propynyloxy, but-3-ynyloxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, NH, CONH, NHCO and OCH_2 and Q^1 is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, tetrahydrofuran-3-yl, 3- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl,

3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CONH, NHCO, CH=CH and C≡C,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of the formula :

$$Q^2\text{-}X^2\text{-}$$

wherein X^2 is a direct bond or is CO, NHCO or N(Me)CO and Q^2 is pyridyl, pyridylmethyl, 2-pyridylethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido or from a group of the formula :

$$-X^3\text{-}Q^3$$

wherein X^3 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^3 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, allyl, 2-propynyl, methoxy, methylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and acetyl, or optionally bears 1 substituent selected from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and NH and R^8 is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, NH and CO and Q^4 is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents; and

(n) m is 1 and the R^1 group is located at the 5-, 6- or 7-position or m is 2 and each R^1 group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R^1 is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl,

ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, but-3-enyloxy, pent-4-enyloxy, hex-5-enyloxy, but-3-ynyloxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, pyrrolidin-1-yl, piperidino, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino, 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and when R^1 is a vinyl or ethynyl group, the R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl, or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^2 is imidazolylmethyl, 2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and methoxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with allyl, 2-propynyl, methylsulphonyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl,

2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(o) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is selected from O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ and $OC(R^4)_2$ wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or X^1 is a direct bond and Q^1 is aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl, or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno groups or a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl,

(2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl and (2-6C)alkanoyl, or optionally bears 1 substituent selected from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(p) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is selected from O, NH, CONH, NHCO and OCH_2 and Q^1 is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, tetrahydrofuran-3-yl, 3- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl,

pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

or wherein X^1 is a direct bond and Q^1 is benzyl, cyclopropylmethyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CONH, NHCO, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^3 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, allyl, 2-propynyl, methoxy, methylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and acetyl, or optionally bears 1 substituent selected from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and NH and R^8 is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, NH and CO and Q^4 is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(q) m is 1 and the R^1 group is located at the 5-, 6- or 7-position or m is 2 and each R^1 group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R^1 is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy,

propoxy, isopropoxy, butoxy, pentyloxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino, 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and methoxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with allyl, 2-propynyl, methylsulphonyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(r) n is 1 or 2 and the R^3 groups, which may be the same or different, are located at the 4-, 5- and/or 6-positions of the 2,3-methylenedioxyphenyl group and are selected from halogeno, trifluoromethyl, cyano, hydroxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl and (1-6C)alkylsulphonyl, or from a group of the formula :

$$-X^6-R^{11}$$

wherein X^6 is a direct bond and R^{11} is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$$-X^7-Q^5$$

wherein X^7 is a direct bond and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may

be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy;

(s) n is 1 or 2 and the R^3 groups, which may be the same or different, are located at the 4-, 5- and/or 6-positions of the 2,3-methylenedioxyphenyl group and are selected from fluoro, chloro, bromo, iodo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, 1-propynyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, hydroxymethyl, 2-hydroxyethyl, 2-methoxyethyl, cyanomethyl, 2-cyanoethyl, aminomethyl, methylaminomethyl, phenyl and benzyl; and

(t) n is 1 or 2 and the R^3 groups, which may be the same or different are located at the 4-, and/or 6 positions of the 2,3-methylenedioxyphenyl group and are selected from chloro, bromo, iodo, methyl, ethynyl, methylthio, hydroxymethyl, 2-cyanoethyl, 2-methoxyethyl, phenyl and benzyl.

Further particular compounds for use according to the invention include, for example, quinoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of Z, m, R^1, n and R^3 has any of the meanings defined hereinbefore provided that :-

(A) R^1 substituents may only be located at the 5-, 6- and/or 7-positions on the quinoline ring *i.e.* the 2- and 8-positions remain unsubstituted; or

(B) R^1 substituents may only be located at the 6- and/or 7-positions on the quinoline ring *i.e.* the 2-, 5- and 8-positions remain unsubstituted.

A further aspect of the invention is the use of quinoline derivative of the Formula I wherein :

Z is O or NH;

m is 1 and the R^1 group is located at the 5-, 6- or 7-position or m is 2 and each R^1 group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R^1 is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,

2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino and acetoxy;

and wherein any heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and N,N-dimethylcarbamoyl and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with allyl, methylsulphonyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents; and

n is 0 or 1 and the R^3 group, if present, is located at the 5- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, methoxy and ethoxy,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

Z is O or NH;

m is 2 and the first R^1 group is located at the 6-position and is selected from hydroxy, methoxy, ethoxy and propoxy, and the second R^1 group is located at the 7-position and is selected from 2-hydroxyethoxy, 3-hydroxypropoxy, 4-hydroxybutoxy, 2-methoxyethoxy, 3-methoxypropoxy, 4-methoxybutoxy, 2-(2-hydroxyethoxy)ethoxy, 2-(2-methoxyethoxy)ethoxy, 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy, 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy, 2-(N-allylamino)ethoxy, 3-(N-allylamino)propoxy, 2-(N-allyl-N-methylamino)ethoxy, 3-(N-allyl-N-methylamino)propoxy, 2-(N-prop-2-ynylamino)ethoxy, 3-(N-prop-2-ynylamino)propoxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy, 3-(N-methyl-N-prop-2-ynylamino)propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 4-(4-allylpiperazin-1-yl)butoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy,

3-(4-methylsulphonylpiperazin-1-yl)propoxy, 4-(4-methylsulphonylpiperazin-1-yl)butoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-1-yl)butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy, 2-methylsulphonylethoxy and 3-methylsulphonylpropoxy,

and wherein any CH_2 group within the second R^1 group that is attached to two carbon atoms optionally bears a hydroxy group or acetoxy group on said CH_2 group,

and wherein any heterocyclyl group within the second R^1 group optionally bears 1 or 2 substituents selected from fluoro, hydroxy, methyl and oxo; and

n is 0 or n is 1 and the R^3 group, if present, is located at the 5- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy and ethoxy,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

Z is O or NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy, 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy, 2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)propoxy, 4-(N-isobutyl-N-methylamino)butoxy, 2-(N-allyl-N-methylamino)ethoxy, 3-(N-allyl-N-methylamino)propoxy, 2-(N-prop-2-ynylamino)ethoxy, 3-(N-prop-2-ynylamino)propoxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy, 3-(N-methyl-N-prop-2-ynylamino)propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy,

3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, N-cyanomethylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, N-cyanomethylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 4-homopiperidin-1-ylbutoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-piperazin-1-ylpropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-piperazin-1-ylbutoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 4-(4-allylpiperazin-1-yl)butoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 4-(4-methylsulphonylpiperazin-1-yl)butoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-1-yl)butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-(2-piperazin-1-ylethoxy)ethoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-tetrahydropyran-4-ylethoxy, 3-tetrahydropyran-4-ylpropoxy, 2-pyrrol-1-ylethoxy, 3-pyrrol-1-ylpropoxy, 2-(2-pyridyloxy)ethoxy, 3-(2-pyridyloxy)propoxy, 2-(3-pyridyloxy)ethoxy, 3-(3-pyridyloxy)propoxy, 2-(4-pyridyloxy)ethoxy, 3-(4-pyridyloxy)propoxy, 2-pyridylmethoxy, 3-pyridylmethoxy and 4-pyridylmethoxy,

and wherein any CH_2 group within the second R^1 group that is attached to two carbon atoms optionally bears a hydroxy group on said CH_2 group,

and wherein any heteroaryl group within the second R^1 group optionally bears 1 or 2 substituents selected from chloro, cyano, hydroxy and methyl, and any heterocyclyl group

within the second R^1 group optionally bears 1 or 2 substituents selected from fluoro, hydroxy, methyl and oxo; and

n is 0 or n is 1 and the R^3 group, if present, is located at the 6-position of the 2,3-methylenedioxyphenyl group and is selected from fluoro, chloro and bromo,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-allylpiperazin-1-yl)propoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 3-chloropropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy; and

n is 0 or n is 1 and the R^3 group, if present, is located at the 6-position of the 2,3-methylenedioxyphenyl group and is selected from chloro and bromo,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

Z is NH or O;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from hydroxy, methoxy, 2-bromoethoxy, 2-hydroxyethoxy, 2-methoxyethoxy, 2-hydroxy-3-methoxypropoxy, 2-(2-hydroxyethoxy)ethoxy, 2-prop-2-ynylaminoethoxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy, 3-(N-methyl-N-prop-2-ynylamino)propoxy, 3-(2,5-dimethylpyrrol-1-yl)propoxy, 3-pyrrolidin-1-ylpropoxy, 3-(3-fluoropyrrolidin-1-yl)propoxy, 3-(3,3-difluoropyrrolidin-1-yl)propoxy, 3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy, 3-morpholinopropoxy, 2-hydroxy-3-morpholinopropoxy, 2-fluoro-3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 3-(4-fluoropiperidin-1-yl)propoxy, 3-(4,4-difluoropiperidin-1-yl)propoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-fluoro-3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-fluoro-3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy,3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-1-yl)butoxy, 3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 3-chloropropoxy and 3-bromopropoxy; and

n is 0, 1 or 2 and each R^3 group, if present, is selected from fluoro, chloro, bromo, iodo, cyano, methyl, ethyl, ethynyl, methylthio, methylsulphonyl, hydroxymethyl, 2-methoxyethyl, 2-cyanoethyl, dimethylaminomethyl, phenyl and benzyl;

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein:

Z is O or NH;

m is 1 and the R^1 group is located at the 6- or 7-position or m is 2 and each R^1 group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R^1 is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino,

diethylamino, acetamido, propionamido, 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino and acetoxy;

and wherein any heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and N,N-dimethylcarbamoyl and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents; and

n is 0 or 1 and the R^3 group, if present, is located at the 5- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, methoxy and ethoxy,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

Z is O or NH;

m is 2 and the first R^1 group is located at the 6-position and is selected from hydroxy, methoxy, ethoxy and propoxy, and the second R^1 group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy, 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy, 2-methylsulphonylethoxy and 3-methylsulphonylpropoxy,

and wherein any CH_2 group within the second R^1 group that is attached to two carbon atoms optionally bears a hydroxy group or acetoxy group on said CH_2 group,

and wherein any heterocyclyl group within the second R^1 group optionally bears 1 or 2 oxo substituents; and

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy and ethoxy,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

Z is O or NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy, 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy, 2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)propoxy, 4-(N-isobutyl-N-methylamino)butoxy, 2-(N-allyl-N-methylamino)ethoxy, 3-(N-allyl-N-methylamino)propoxy, 4-(N-allyl-N-methylamino)butoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, N-cyanomethylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, N-cyanomethylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy,

3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 4-homopiperidin-1-ylbutoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-piperazin-1-ylpropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-piperazin-1-ylbutoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-(2-piperazin-1-ylethoxy)ethoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-tetrahydropyran-4-ylethoxy, 3-tetrahydropyran-4-ylpropoxy, 2-pyrrol-1-ylethoxy, 3-pyrrol-1-ylpropoxy, 2-(2-pyridyloxy)ethoxy, 3-(2-pyridyloxy)propoxy, 2-(3-pyridyloxy)ethoxy, 3-(3-pyridyloxy)propoxy, 2-(4-pyridyloxy)ethoxy, 3-(4-pyridyloxy)propoxy, 2-pyridylmethoxy, 3-pyridylmethoxy and 4-pyridylmethoxy,

and wherein any CH_2 group within the second R^1 group that is attached to two carbon atoms optionally bears a hydroxy group on said CH_2 group,

and wherein any heteroaryl group within the second R^1 group optionally bears 1 or 2 substituents selected from chloro, cyano, hydroxy and methyl, and any heterocyclyl group within the second R^1 group optionally bears 1 or 2 substituents selected from hydroxy, methyl and oxo; and

n is 0 or n is 1 and the R^3 group is located at the 6-position of the 2,3-methylenedioxyphenyl group and is selected from chloro and bromo,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of quinoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy,

piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 3-chloropropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy; and

n is 0 or n is 1 and the R^3 group is located at the 6-position of the 2,3-methylenedioxyphenyl group and is selected from chloro and bromo,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of quinoline derivative of the Formula I wherein:

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from methoxyl, 2-hydroxyethoxy, 2-(2-hydroxyethoxy)ethoxy, 2-methoxyethoxy, 2-prop-2-ynylaminoethoxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy, 3-(N-methyl-N-prop-2-ynylamino)propoxy, 3-pyrrolidin-1-ylpropoxy, 3-(3-fluoropyrrolidin-1-yl)propoxy, 3-(3,3-difluoropyrrolidin-1-yl)propoxy, 3-(4-fluoropiperidin-1-yl)propoxy, 3-(4,4-difluoropiperidin-1-yl)propoxy, 3-morpholinopropoxy, (2R)-2-hydroxy-3-morpholinopropoxy, (2S)-2-fluoro-3-morpholinopropoxy, 3-piperidonopropoxy, 3-(4-hydroxypiperidin-1-yl) propoxy, 3-(piperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, (2R)-3-(4-acetylpiperazin-1-yl)2-hydroxypropoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxyl, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, (2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy3-(4-allylpiperazin-1-yl)propoxy, 3-(4-allylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)butoxyl, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxyl,

3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy, 3-(2,5-dimethyl-3-pyrrol-1-yl)propoxy, (2S)-2-fluoro-3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, and 3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy;

n is 0, 1 or 2 and R^3 group is located at the 4- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from chloro, bromo, iodo, methyl, methylthio, ethynyl, phenyl, benzyl, hydroxymethyl, 2-cyanoethyl, methoxyethyl or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of quinoline derivative of the Formula I wherein:

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from methoxyl, 3-(N-methyl-N-prop-2-ynylamino)propoxy 3-pyrrolidin-1-ylpropoxy, 3-(3,3-difluoropyrrolidin-1-yl)propoxy, 3-(4-fluoropiperidin-1-yl)propoxy, 3(4,4-difluoropiperidin-1-yl)propoxy, 3-(4-hydroxypiperidin-1-yl) propoxy, 3-morpholinopropoxy, (2S)-2-fluoro-3-morpholinopropoxy, 3-piperidonopropoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxyl, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-allylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)butoxyl, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxyl, (2S)-2-fluoro-3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy and 3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy;

n is 0 or n is 1 and R^3 group is located at the 4- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from chloro, bromo, iodo, methyl, phenyl, benzyl, hydroxymethyl, 2-cyanoethyl, methoxyethyl or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of quinoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from 3-(4-methylpiperazin-1-yl)propoxy or 3-chloropropoxy,

n is 1 and the R^3 group is a chloro or bromo group located at the 6-position of the 2,3-methylenedioxyphenyl group,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

Further particular compounds for use according to the invention include, for example, the quinoline derivatives of the Formula I described hereinafter in Examples 3(1) to 3(12), 3(27), 3(29), 3(32), 6(6), 6(7), 6(11), 6(14), 6(16), 6(18), 6(19), 6(21), 6(22), 10, 14 and 16.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

m is 2 and the first R^1 group is located at the 5-position and is selected from tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, N-methylazetidin-3-yloxy, N-ethylazetidin-3-yloxy, N-isopropylazetidin-3-yloxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy, N-prop-2-ynylpiperidin-4-yloxy, N-acetylpiperidin-4-yloxy, N-methylsulphonylpiperidin-4-yloxy, N-(2-methoxyethyl)piperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

and the second R^1 is located at the 7-position and is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, benzyloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,

2-[(2S)-2-carbamoylpyrrolidin-1-yl]ethoxy, 2-[(2S)-2-(N-methylcarbamoyl)pyrrolidin-1-yl]ethoxy, 2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidin-1-yl]ethoxy, 2-tetrahydropyran-4-ylethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-(4-pyridyloxy)ethoxy, 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy and 3-cyanopyrid-4-ylmethoxy;

and wherein any CH_2 group within a R^1 substituent that is attached to two carbon atoms optionally bears a hydroxy group on said CH_2 group, and wherein any heterocyclyl group within a R^1 substituent optionally bears 1 or 2 oxo substituents,

and wherein any CH_2 group within a R^1 substituent that is attached to two carbon atoms optionally bears a hydroxy group on said CH_2 group;

n is 0 or n is 1 and the R^3 group, if present, is located at the 5- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy and ethoxy,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

m is 2 and the first R^1 group is located at the 5-position and is selected from tetrahydropyran-4-yloxy, N-methylpyrrolidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, piperidin-4-ylmethoxy and N-methylpiperidin-4-ylmethoxy,

and the second R^1 is located at the 7-position and is selected from methoxy, benzyloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy and 3-methylsulphonylpropoxy;

n is 0 or n is 1 and the R^3 group, if present, is located at the 6-position of the 2,3-methylenedioxyphenyl group and is selected from chloro and bromo,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

m is 2 and the first R^1 group is located at the 5-position and is selected from tetrahydropyran-4-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, piperidin-4-ylmethoxy and N-methylpiperidin-4-ylmethoxy, and the second R^1 is located at the 7-position and is selected from methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, benzyloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 3-methylsulphonylpropoxy, piperidin-4-ylmethoxy and N-methylpiperidin-4-ylmethoxy; n is 0 or n is 1 and the R^3 group, if present, is located at the 6-position of the 2,3-methylenedioxyphenyl group and is selected from chloro and bromo, or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I wherein :

m is 2 and the first R^1 group is located at the 5-position and is selected from tetrahydropyran-4-yloxy, N-methylpiperidin-4-yloxy, and the second R^1 is located at the 7-position and is selected from methoxy and 3-morpholinopropoxy, n is 0, 1 or 2 and each R^3 group, if present, is located at the 4 and/or 6-position of the 2,3-methylenedioxyphenyl group and is independently selected from chloro and bromo, or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A further aspect of the invention is the use of a quinoline derivative of the Formula I selected from:-

4-(4-iodo-2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl) propoxy]quinoline;

4-(4-benzyl-2,3-methylenedioxyanilino)-3-cyano-6,7-dimethoxyquinoline;

4-(4-bromo-2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline;

4-(2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylsulphonylpiperazin-1-yl)propoxy]quinoline;

4-(2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy]quinoline;

4-[4-(2-methoxyethyl)-2,3-methylenedioxyanilino]-3-cyano-6,7-dimethoxyquinoline;

4-[4-(2-methoxyethyl)-2,3-methylenedioxyanilino]-3-cyano-6-methoxy-7-[3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy]quinoline; and

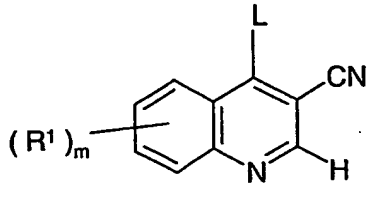
4-[4-(2-methoxyethyl)-2,3-methylenedioxyanilino]-3-cyano-6-methoxy 7-(3-morpholinopropoxy)quinoline,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solidl tumour disease.

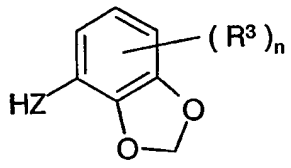
A quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, for use in the invention, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes are illustrated by the following representative process variants in which, unless otherwise stated, m, R^1, Z, n and R^3 have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) For the production of those compounds of the Formula I wherein Z is an O, S or $N(R^2)$, the reaction of a quinoline of the Formula II



II

wherein L is a displaceable group and m and R^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula III



III

wherein Z is O, S, or N(R^2) and n, R^3 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction may conveniently be carried out in the presence of a suitable acid or in the presence of a suitable base. A suitable acid is, for example, an inorganic acid such as, for example, hydrogen chloride or hydrogen bromide. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal amide, for example sodium hexamethyldisilazane, or, for example, an alkali metal hydride, for example sodium hydride.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 250°C, preferably in the range 0 to 120°C.

Typically, the quinoline of the Formula II may be reacted with a compound of the Formula III in the presence of an aprotic solvent such as N,N-dimethylformamide, conveniently in the presence of a base, for example potassium carbonate or sodium

hexamethyldisilazane, and at a temperature in the range, for example, 0 to 150°C, preferably in the range, for example, 0 to 70°C.

The quinoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and

1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

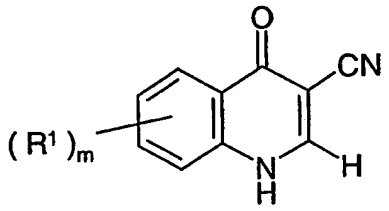
Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

Quinoline starting materials of the Formula II may be obtained by conventional procedures such as those disclosed in International Patent Applications WO 98/43960 and WO 00/68201. For example, a 1,4-dihydroquinolin-4-one of Formula IV



IV

wherein m and R^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

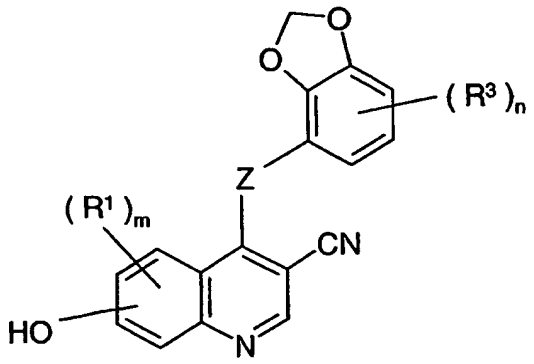
The 4-chloroquinoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as N,N-dimethylformamide.

2,3-Methylenedioxyanilino starting materials (Formula III, for example when Z is NH) and 2,3-methylenedioxyphenol starting materials (Formula III when Z is O) may be obtained by conventional procedures as illustrated in the Examples. Corresponding 2,3-methylenedioxythiophenol starting materials (Formula III, when Z is S) may be obtained by conventional procedures.

(b) For the production of those compounds of the Formula I wherein at least one R^1 group is a group of the formula

$$Q^1\text{-}X^1\text{-}$$

wherein Q^1 is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X^1 is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of a quinoline of the Formula V



V

wherein m, R^1, Z, n and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by conventional means.

A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of an azo compound such as diethyl or di-tert-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

(c) For the production of those compounds of the Formula I wherein R^1 is an amino-substituted (1-6C)alkoxy group (such as 2-homopiperidin-1-ylethoxy or 3-dimethylaminopropoxy), the reaction of a compound of the Formula I wherein R^1 is a halogeno-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(d) For the production of those compounds of the Formula I wherein R^1 is a hydroxy group, the cleavage of a quinoline derivative of the Formula I wherein R^1 is a (1-6C)alkoxy or arylmethoxy group.

The cleavage reaction may conveniently be carried out by any of the many procedures known for such a transformation. The cleavage reaction of a compound of the Formula I wherein R^1 is a (1-6C)alkoxy group may be carried out, for example, by treatment of the quinoline derivative with an alkali metal (1-6C)alkylsulphide such as sodium ethanethiolate or, for example, by treatment with an alkali metal diarylphosphide such as lithium diphenylphosphide. Alternatively the cleavage reaction may conveniently be carried out, for

example, by treatment of the quinoline derivative with a boron or aluminium trihalide such as boron tribromide. The cleavage reaction of a compound of the Formula I wherein R^1 is a arylmethoxy group may be carried out, for example, by hydrogenation of the quinoline derivative in the presence of a suitable metallic catalyst such as palladium or by reaction with an organic or inorganic acid, for example trifluoroacetic acid. Such reactions are preferably carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

(e) For the production of those compounds of the Formula I wherein an R^1 group contains a primary or secondary amino group, the cleavage of the corresponding compound of the Formula I wherein the R^1 group contains a protected primary or secondary amino group.

Suitable protecting groups for an amino group are, for example, any of the protecting groups disclosed hereinbefore for an amino group. Suitable methods for the cleavage of such amino protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkoxycarbonyl group such as a tert-butoxycarbonyl group which may be cleaved under conventional reaction conditions such as under acid-catalysed hydrolysis, for example in the presence of trifluoroacetic acid.

(f) For the production of those compounds of the Formula I wherein an R^1 group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of a quinoline derivative of the formula I wherein the R^1 group contains a hydroxy group or a primary or secondary amino group as appropriate.

A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide, conveniently in the presence of a suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature.

Conveniently for the production of those compounds of the Formula I wherein R^1 contains a (1-6C)alkylamino or substituted (1-6C)alkylamino group, a reductive amination reaction may be employed. For example, for the production of those compounds of the

Formula I wherein R^1 contains a N-methyl group, the corresponding compound containing a N-H group may be reacted with formaldehyde in the presence of a suitable reducing agent. A suitable reducing agent is, for example, a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. The reaction is performed at a temperature in the range, for example, 10 to 80°C, conveniently at or near ambient temperature.

(g) For the production of those compounds of the Formula I wherein R^1 is an amino-hydroxy-disubstituted (1-6C)alkoxy group (such as 2-hydroxy-3-pyrrolidin-1-ylpropoxy or 3-[N-allyl-N-methylamino]-2-hydroxypropoxy), the reaction of a compound of the Formula I wherein the R^1 group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

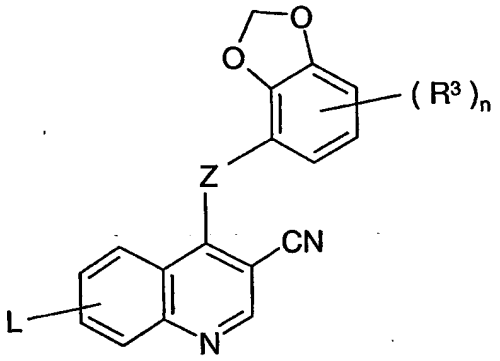
(h) For the production of those compounds of the Formula I wherein an R^1 group contains a hydroxy group, the cleavage of the corresponding compound of the Formula I wherein the R^1 group contains a protected hydroxy group.

Suitable protecting groups for a hydroxy group are, for example, any of the protecting groups disclosed hereinbefore. Suitable methods for the cleavage of such hydroxy protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkanoyl group such as an acetyl group which may be cleaved under conventional reaction conditions such as under base-catalysed conditions, for example in the presence of ammonia.

(i) For the production of those compounds of the Formula I wherein Z is a SO or SO_2 group, the oxidation of a compound of Formula I wherein Z is a S group.

Conventional oxidation reagents and reaction conditions for such partial or complete oxidation of a sulphur atom are well known to the organic chemist.

(j) For the production of those compounds of the Formula I wherein an R^1 group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of a quinoline derivative of the Formula VI



VI

wherein L is a displaceable group as defined hereinbefore and Z, n and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an alcohol or amine as appropriate.

(k) The conversion of a compound of the Formula I wherein an R^1 or R^3 substituent is a halogeno group into a further compound of the Formula I wherein the R^1 or R^3 substituent is, for example, a cyano, ethynyl or phenyl group.

For example, a compound of the Formula I wherein an R^1 or R^3 substituent is a halogeno group may be reacted with a metal cyanide to form a compound of the Formula I wherein an R^1 or R^3 substituent is a cyano group. Conveniently, the reaction may be carried out in the presence of a suitable catalyst. A suitable metal cyanide is, for example, a heavy metal cyanide such as zinc cyanide. A suitable catalyst is, for example, an organometallic reagent, for example an organoiron compound such as diphenylphosphinoferrocene. The conversion reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 100°C.

For example, a compound of the Formula I wherein an R^1 or R^3 substituent is a halogeno group may be reacted with a (2-6C)alkyne to form a compound of the Formula I wherein an R^1 or R^3 substituent is a (2-6C)alkynyl group such as an ethynyl group. The

reaction may conveniently be carried out in the presence of a suitable base as defined hereinbefore and in the presence of a suitable catalyst. For this conversion, a suitable catalyst is, for example, an organometallic reagent, for example an organopalladium compound such as tetrakis(triphenylphosphine)palladium(0). The conversion reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 60°C.

For example, a compound of the Formula I wherein an R^1 or R^3 substituent is a halogeno group may be reacted with an arylboron reagent to form a compound of the Formula I wherein an R^1 or R^3 substituent is an aryl group such as a phenyl group. A suitable arylboron reagent is, for example, an arylboronic acid. The reaction may conveniently be carried out in the presence of a suitable catalyst, for example, an organopalladium compound such as tetrakis(triphenylphosphine)palladium(0). The conversion reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 80°C.

When a pharmaceutically-acceptable salt of a quinoline derivative of the Formula I is required, for example an acid-addition salt, for use according to the invention it may be obtained by, for example, reaction of said quinoline derivative with a suitable acid using a conventional procedure.

Biological Assays

The following assays can be used to measure the effects of the compounds as inhibitors of the MAPK pathway.

Assay to detect MEK inhibition

To evaluate inhibitors of the MAPK pathway a coupled assay was carried out which measures phosphorylation of serine/threonine residues present in the substrate in the presence or absence of inhibitor. Recombinant glutathione S-transferase fusion protein containing human p45MEK1 (GST-MEK) was activated by c-raf (Sf9 insect cell lysate from triple baculoviral infection with c-raf/ras/lck) and used for the assay. Active GST-MEK was first used to activate a recombinant glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) in the presence of ATP and Mg^{2+} for 60min at room temperature in the presence or absence of potential inhibitors. The activated GST-MAPK was then incubated with myelin basic protein (MBP) as substrate for 10min at room temperature in the presence of ATP, Mg^{2+} and ^{33}P-ATP. The reaction was stopped by addition of 20% v/v phosphoric

acid. Incorporation of ^{33}P into the myelin basic protein was determined by capture of the substrate on a filter mat, washing and counting using scintillation methods. The extent of inhibition was determined by comparison with untreated controls.

The final assay solution contained 10mM Tris, pH 7.5, 0.05mM EGTA, 8.33μM [$\gamma^{33}P$]ATP, 8.33mM $Mg(OAc)_2$, 0.5mM sodium orthovanadate, 0.05%w/v BSA, 6.5ng GST-MEK, 1μg GST-MAPK and 16.5μg MBP in a reaction volume of 60μl.

Compounds tested had IC_{50} results typically less than 0.5μM.

In vitro MAP kinase assay

To determine whether compounds were inhibiting GST-MEK or GST-MAPK, a direct assay of MAPK activity was employed. GST-MAPK was activated by a constitutively active GST-MEK fusion protein containing two point mutations (S217E, S221E) and used for the assay in the presence and absence of potential inhibitors. The activated GST-MAPK was incubated with substrate (MBP) for 60min at room temperature in the presence of ATP, Mg^{2+} and ^{33}P-ATP. The reaction was stopped by addition of 20% v/v phosphoric acid. Incorporation of ^{33}P into the myelin basic protein was determined by capture of the substrate on a filter mat, washing and counting using scintillation methods.

The final assay solution contained 12mM Tris, pH 7.5, 0.06mM EGTA, 30μM [$\gamma^{33}P$]ATP, 10mM $Mg(OAc)_2$, 0.6mM sodium orthovanadate, 0.06%w/v BSA, 28ng GST-MAPK and 16.5μg MBP in a reaction volume of 60μl.

Compounds of Formula I showed activity in this screen.

Cell proliferation assays

Cells were seeded into multi-well plates at 20 000 - 40 000 cells/ml in growth medium containing 5% FCS and incubated overnight at 37°C. The compounds were prepared in fresh medium at an appropriate concentration and added to the wells containing the cells. These were then incubated for a further 72 hours. Cells were then either removed from the wells by incubating with trypsin/EDTA and counted using a Coulter counter, or treated with XTT/PMS in PBSA and optical densities read at 450nm. Compounds of Formula I had IC_{50} results typically less than 30μM.

A pharmaceutical composition for the use of compounds of Formula I according to the invention comprises a quinoline derivative of the Formula I, or a pharmaceutically-

acceptable salt thereof, as defined hereinbefore, in association with a pharmaceutically-acceptable diluent or carrier.

Thus, according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

The compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses

will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

The anti-proliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl

transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or

separate dosing of the individual components of the treatment. Such combination products employ the compounds of the Formula I within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided the use of a pharmaceutical product comprising a quinoline derivative of the Formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the use in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of MEK enzyme. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following Examples in which, generally :

(i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields, where present, are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Jeol JNM EX 400 spectrometer operating at a field strength of 400MHz, Varian Gemini 2000 spectrometer operating at a field strength of

300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture;

(viii) where certain compounds were obtained as an acid-addition salt, for example a mono hydrochloride salt or a dihydrochloride salt, the stoichiometry of the salt was based on the number and nature of the basic groups in the compound, the exact stoichiometry of the salt was generally not determined, for example by means of elemental analysis data;

(ix) the following abbreviations have been used:-

DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran
DMA	N,N-dimethylacetamide

The compounds described in the following examples were tested in the assays described above and found to be active.

Example 1

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline

Sodium hexamethyldisilazane (1M solution in THF; 3.34 ml) was added to a solution of 6-chloro-2,3-methylenedioxyaniline (0.573 g) in DMF (12 ml) that was cooled to 0°C and the mixture was stirred for 5 minutes. A solution of 4-chloro-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline (0.5 g) in DMF (3 ml) was added and the resultant mixture was stirred at ambient temperature for 1 hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained the title compound as a solid (0.62 g); NMR Spectrum: (DMSOd_6 at 60°C) 2.32

(m, 2H), 3.9 (m, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 6.1 (s, 2H), 7.0 (d, 1H), 7.1 (d, 1H), 7.4 (s, 1H), 7.9 (s, 1H), 8.42 (s, 1H), 9.32 (s, 1H); Mass Spectrum: $M+H^+$ 446 and 448.

The 4-chloro-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline used as a starting material was prepared as follows :-

A mixture of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (0.2 g, prepared as described in International Patent Application WO 00/68201, disclosed as compound (7) within Preparation 1 therein), potassium tert-butoxide (0.1 g) and DMF (8 ml) was stirred at ambient temperature for 15 minutes. 1-Bromo-3-chloropropane (0.134 g) was added and the reaction mixture was stirred at ambient temperature for 16 hours. The resultant mixture was evaporated and the residue was partitioned between methylene chloride and an aqueous sodium bicarbonate solution. The organic layer was dried using magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of ethyl acetate and hexane. There was thus obtained the required starting material (0.131 g); NMR Spectrum: ($DMSOd_6$) 2.3 (m, 2H), 3.8 (m, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 7.42 (s, 1H), 7.68 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 311.

The 6-chloro-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

Sulphuryl chloride (72.5 ml) was added dropwise during 1.7 hours to a stirred mixture of benzodioxole (100 g), aluminium trichloride (0.43 g) and diphenyl sulphide (0.55 ml). Once the reaction started with the evolution of sulphur dioxide, the reaction mixture was cooled in a water bath to a temperature of approximately 22°C. After completion of the addition, the reaction mixture was stirred at ambient temperature for 45 minutes. The reaction mixture was degassed under vacuum and filtered and the filtrate was distilled at atmospheric pressure using a Vigreux distillation column. There was thus obtained 5-chloro-1,3-benzodioxole; b.p. 185-187°C; NMR Spectrum: ($CDCl_3$) 6.0 (s, 2H); 6.7 (d, 1H); 6.75-6.9 (m, 2H).

A mixture of diisopropylamine (4.92 ml) and THF (100 ml) was cooled to -78°C and n-butyllithium (2.5 M in hexane, 14 ml) was added dropwise. The mixture was stirred at -78°C for 15 minutes. 5-Chloro-1,3-benzodioxole (3.73 ml) was added dropwise and the reaction mixture was stirred at -78°C for 30 minutes. Dry carbon dioxide gas was bubbled into the reaction mixture for 30 minutes. The resultant reaction mixture was allowed to warm to ambient temperature and was stirred for a further hour. Water was added and the organic

solvent was evaporated. The residue was acidified to pH2 by the addition of 2N aqueous hydrochloric acid solution. The resultant solid was isolated and washed in turn with water and diethyl ether. There was thus obtained 5-chloro-1,3-benzodioxole-4-carboxylic acid (5.4 g); NMR Spectrum: ($DMSOd_6$) 6.15 (s, 2H), 7.0 (m, 2H), 13.7 (br s, 1H).

A portion (1 g) of the material so obtained was dissolved in 1,4-dioxane (15 ml) and anhydrous tert-butanol (4 ml), diphenylphosphoryl azide (1.12 ml) and triethylamine (0.73 ml) were added in turn. The resultant mixture was stirred and heated to 100°C for 4 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and a5% aqueous citric acid solution. The organic phase was washed in turn with water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl N-(5-chloro-1,3-benzodioxol-4-yl)carbamate (1.1 g); NMR Spectrum: ($DMSOd_6$) 1.45 (s, 9H), 6.1 (s, 2H), 6.85 (d, 1H), 6.95 (d, 1H), 8.75 (s, 1H).

A mixture of the material so obtained (1.1 g), trifluoroacetic acid (6 ml) and methylene chloride (20 ml) was stirred at ambient temperature for 3 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 6-chloro-2,3-methylenedioxyaniline (0.642 g); NMR Spectrum: ($DMSOd_6$) 5.15 (s, 2H), 6.0 (s, 2H), 6.25 (d, 1H), 6.75 (d, 1H).

Example 2

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline

A mixture of 4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline (0.1 g), N-methylpiperazine (0.075 ml) and DMF (2 ml) was stirred and heated to 60°C for 24 hours. The cooled mixture was evaporated and the resultant residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained the title compound (0.051 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.35 (m, 2H), 2.95 (s, 3H), 3.45 (m, 2H), 3.2-4.0 (m, 8H), 4.02 (s, 3H), 4.32 (m, 2H), 6.15 (m, 2H), 7.08 (d, 1H), 7.15 (d, 1H), 7.48 (s, 1H), 8.15 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 511.

Example 3

Using an analogous procedure to that described in Example 2, the appropriate 7-(ω-haloalkoxy)-3-cyanoquinoline was reacted with the appropriate amine or heterocycle to give the compounds described in Table I.

One example of an appropriate 7-(ω-haloalkoxy)-3-cyanoquinoline is 7-(3-chloropropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline. This was prepared as follows:-

Using an analogous procedure to that described in Example 1, 4-chloro-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline was reacted with 2,3-methylenedioxyaniline to give the title compound as a solid (0.62 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.4 (m, 2H), 3.85 (m, 2H), 3.95 (s, 3H), 4.3 (m, 2H), 6.0 (s, 2H), 6.8-7.0 (m, 2H), 7.35 (s, 1H), 7.8 (s, 1H), 8.45 (s, 1H), 9.6 (br s, 1H); Mass Spectrum: $M+H^+$ 412.

The 2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 2,3-dihydroxybenzoic acid (5 g), methanol (50 ml) and concentrated sulphuric acid (10 drops) was stirred and heated to 60°C for 24 hours. The mixture was evaporated and the residue was taken up in ethyl acetate. The organic solution was washed with a saturated solution of sodium bicarbonate, dried over magnesium sulphate and evaporated to give methyl 2,3-dihydroxybenzoate (2.19 g); NMR Spectrum: ($CDCl_3$) 3.95 (s, 3H), 5.7 (s, 1H), 6.8 (t, 1H), 7.15 (d, H), 7.35 (d, H).

After repetition of the previous reaction, a mixture of methyl 2,3-dihydroxybenzoate (2.8 g), potassium fluoride (4.8 g) and DMF (45 ml) was stirred at ambient temperature for 30 minutes. Dibromomethane (1.28 ml) was added and the mixture was heated to 120°C for 3 hours. The mixture was cooled to ambient temperature, poured into water and extracted with diethyl ether. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained methyl 2,3-methylenedioxybenzoate (2.3 g) as a solid; NMR Spectrum: ($CDCl_3$) 3.95 (s, 3H), 6.1 (s, 2H), 6.85 (t, 1H), 7.0 (d, 1H), 7.45 (d, 1H).

A mixture of the material so obtained, a 2N aqueous potassium hydroxide solution (15.5 ml) and methanol (40 ml) was stirred at ambient temperature for 2 hours. The solution was concentrated to about one quarter of the original volume and cooled in an ice bath. The

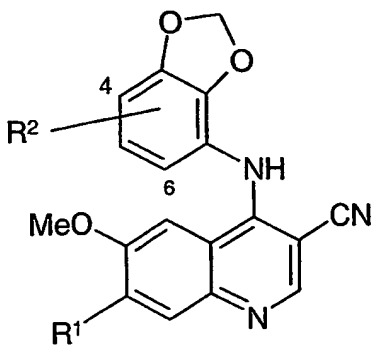
mixture was acidified to pH3.5 by the addition of a 2N aqueous hydrochloric acid solution. The resultant precipitate was collected by filtration and washed in turn with water and diethyl ether. There was thus obtained 2,3-methylenedioxybenzoic acid (1.87 g); NMR Spectrum: ($DMSOd_6$) 6.1 (s, 1H), 6.9 (t, 1H), 7.15 (d, 1H), 7.3 (d, 1H), 13.0 (br s, 1H).

The material so obtained was suspended in anhydrous dioxane (30 ml) and anhydrous diphenylphosphoryl azide (2.45 ml), triethylamine (1.6 ml) and tert-butanol (9 ml) were added. The mixture was heated to reflux for 5 hours. The mixture was cooled to ambient temperature, concentrated by evaporation and diluted with ethyl acetate. The organic phase was washed in turn with a 5% aqueous citric acid solution, water, an aqueous sodium bicarbonate solution and brine and dried over magnesium sulphate. The solvent was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl N-(2,3-methylenedioxyphenyl)carbamate (1.98 g) as a solid; NMR Spectrum: ($CDCl_3$) 1.55 (s, 9H), 5.95 (s, 2H), 6.4 (br s, 1H), 6.55 (d, 1H), 6.8 (t, 1H), 7.45 (d, 1H).

A 5N aqueous hydrochloric acid solution (30 ml) was added to a solution of tert-butyl N-(2,3-methylenedioxyphenyl)carbamate (1.9 g) in ethanol (38 ml) and the reaction mixture was stirred at ambient temperature for 20 hours. The ethanol was evaporated and the residual aqueous phase was washed with diethyl ether and neutralised to pH7 by the addition of solid potassium hydroxide. The resultant mixture was filtered and the aqueous phase was extracted with diethyl ether. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 2,3-methylenedioxyaniline (1.0 g) as an oil; NMR Spectrum: ($CDCl_3$) 3.0 (br s, 2H), 5.9 (s, 2H), 6.3 (m, 2H), 7.25 (t, 1H).

Unless otherwise stated, each compound described in Table I was obtained as a free base.

Table I



Compound No. & Note	R^1	R^2
[1]	3-(4-hydroxypiperidin-1-yl)propoxy	6-chloro
[2]	3-morpholinopropoxy	6-chloro
[3]	3-piperidinopropoxy	6-chloro
[4]	3-pyrrolidin-1-ylpropoxy	6-chloro
[5]	3-(4-acetylpiperazin-1-yl)propoxy	6-chloro
[6]	3-(4-methylsulphonylpiperazin-1-yl)propoxy	6-chloro
[7]	3-(4-cyanomethylpiperazin-1-yl)propoxy	6-chloro
[8]	3-(4-allylpiperazin-1-yl)propoxy	6-chloro
[9]	3-(4-methylpiperazin-1-yl)propoxy	hydrogen
[10]	3-(4-hydroxypiperidin-1-yl)propoxy	hydrogen
[11]	3-(4-acetylpiperazin-1-yl)propoxy	hydrogen
[12]	3-(4-methylsulphonylpiperazin-1-yl)propoxy	hydrogen
[13]	3-(4-allylpiperazin-1-yl)propoxy	hydrogen
[14]	3-(N-methyl-N-prop-2-ynylamino)propoxy	hydrogen
[15]	2-(4-methylpiperazin-1-yl)ethoxy	hydrogen
[16	2-(4-acetylpiperazin-1-yl)ethoxy	hydrogen

[17]	2-(4-allylpiperazin-1-yl)ethoxy	hydrogen
[18]	2-prop-2-ynylaminoethoxy	hydrogen
[19]	2-(N-methyl-N-prop-2-ynylamino)ethoxy	hydrogen
[20]	3-(3-fluoropyrrolidin-1-yl)propoxy	hydrogen
[21]	3-(3,3-difluoropyrrolidin-1-yl)propoxy	hydrogen
[22]	3-(4-fluoropiperidin-1-yl)propoxy	hydrogen
[23]	3-(4,4-difluoropiperidin-1-yl)propoxy	hydrogen
[24]	4-(4-methylpiperazin-1-yl)butoxy	hydrogen
[25]	4-(4-acetylpiperazin-1-yl)butoxy	6-chloro
[26]	3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy	hydrogen
[27]	4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy	hydrogen
[28]	3-(2,5-dimethylpyrrol-1-yl)propoxy	hydrogen
[29]	3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy	hydrogen
[30]	(2S)-2-fluoro-3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy	hydrogen
[31]	(2S)-2-fluoro-3-morpholinopropoxy	hydrogen
[32]	3-morpholinopropoxy	4-(2-methoxyethyl)

Notes

[1] 4-Hydroxypiperidine was used as the heterocycle reactant. The reaction product was purified by column chromatography on reversed-phase silica using decreasingly polar mixtures of acetonitrile and a 1% solution of acetic acid in water. The material so obtained was dissolved in methylene chloride and the solution was dried over magnesium sulphate. The solution was filtered, the filtrate was evaporated and the residue was triturated under a mixture of pentane and diethyl ether. The resultant precipitate was isolated and dried under vacuum. The product contained one equivalent of acetic acid and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.5-1.7 (m, 1H), 1.8-1.95 (m, 2H), 1.95-2.1 (m, 1H), 2.2-2.35 (m, 2H), 3.05 (m, 1H), 3.15-3.45 (m, 4H), 3.55 (d, 1H), 3.7 (m, 1H), 4.0 (s, 3H), 4.3 (m, 2H), 6.15 (d, 2H), 7.08 (d, 1H), 7.15 (d, 1H), 7.45 (s, 1H), 8.15 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 511.

[2] Morpholine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 2.35 (m, 2H), 3.2 (m, 2H), 3.4 (m, 2H), 3.6 (d, 2H), 3.75 (m, 2H), 4.05 (s, 3H), 4.08 (d, 2H), 4.35 (m, 2H), 6.2 (d, 2H), 7.15 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 497 and 499.

[3] Piperidine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 1.45 (m, 1 H), 1.65-1.8 (m, 3H), 1.9 (d, 2H), 2.35 (m, 2H), 3.0 (m, 2H), 3.31 (m, 2H), 3.6 (d, 2H), 4.05 (s, 3H), 4.38 (m, 2H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 495 and 497.

[4] Pyrrolidine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 1.9-2.0 (m, 2H), 2.1 (m, 2H), 2.35 (m, 2H), 3.05-3.2 (m, 2H), 3.45 (m, 2H), 3.75 (m, 2H), 4.08 (s, 3H), 4.35 (m, 2H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 481 and 483.

[5] 1-Acetylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 2.1 (s, 3H), 2.38 (m, 2H), 2.95-3.1 (m, 2H), 3.2 (m, 1H), 3.35-3.55 (m, 3H), 3.65 (d, 2H), 4.08 (s, 3H), 4.05-4.15 (m, 1H), 4.35 (m, 2H), 4.58 (d, 1H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 538.

[6] 1-Methylsulphonylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 2.3-2.4 (m, 2H), 3.08 (s, 3H), 3.12-3.35 (m, 4H), 3.45 (m, 2H), 3.75 (d, 2H), 3.85 (d, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 6.2 (d, 2H), 7.15 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 574 and 576.

The 1-methylsulphonylpiperazine used as a starting material was prepared as follows :-

Mesyl chloride (0.966 ml) was added dropwise to a stirred mixture of 1-benzylpiperazine (2 g), triethylamine (1.74 ml) and methylene chloride (30 ml) which was cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. The mixture was partitioned between methylene chloride and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 7:3 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 1-benzyl-4-

methylsulphonylpiperazine (2.5 g) as a solid; NMR Spectrum: ($CDCl_3$) 2.6 (m, 4H), 2.8 (s, 3H), 3.3 (m, 4H), 3.55 (s, 2H), 7.3 (m, 5H); Mass Spectrum: $M+H^+$ 255.

A mixture of the material so obtained, cyclohexene (30 ml), palladium oxide on charcoal catalyst (20%; 0.5 g) and ethanol (70 ml) was stirred and heated to 80°C for 4 hours. The catalyst was removed by filtration and the solvent was evaporated to give 1-methylsulphonylpiperazine (1.58 g) as a solid; NMR Spectrum: ($CDCl_3$) 2.8 (s, 3H), 3.0 (m, 4H), 3.2 (m, 4H); Mass Spectrum: $M+H^+$ 165.

[7] 1-Cyanomethylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3-2.4 (m, 2H), 2.65-2.8 (m, 2H), 3.05-3.15 (m, 2H), 3.15-3.3 (m, 2H), 3.4 (m, 2H), 3.7 (br s, 2H), 3.9 (s, 2H), 4.1 (s, 3H), 4.35 (m, 2H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 535 and 537.

The 1-cyanomethylpiperazine used as a starting material was prepared as follows :-

A mixture of 1-(tert-butoxycarbonyl)piperazine (5 g), 2-chloroacetonitrile (1.9 ml), potassium carbonate (4 g) and DMF (20 ml) was stirred at ambient temperature for 16 hours. A saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using diethyl ether as eluent. There was thus obtained 1-(tert-butoxycarbonyl)-4-cyanomethylpiperazine as a solid (5.7 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.5 (m, 4H), 3.45 (m, 4H), 3.55 (s, 2H).

A mixture of the material so obtained, trifluoroacetic acid (20 ml) and methylene chloride (25 ml) was stirred at ambient temperature for 4 hours. The mixture was evaporated, toluene was added and the mixture was evaporated again. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 1-cyanomethylpiperazine trifluoroacetate salt which was treated with solid sodium bicarbonate in a mixture of methylene chloride, ethyl acetate and methanol to give the free base form (2.9 g); NMR Spectrum: ($CDCl_3$ and $DMSOd_6$) 2.7 (m, 4H), 3.2 (m, 4H), 3.6 (s, 2H), 6.2 (br s, 1H).

[8] 1-Allylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3-2.4 (m, 2H), 3.5 (m, 2H), 3.45-3.9 (m, 8H), 3.95 (d, 2H), 4.08 (s, 3H), 4.38 (m, 2H), 5.6-5.7 (m, 2H), 5.9-6.0

(m, 1H), 6.2 (d, 2H), 7.1 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 536 and 538.

[9] 1-Methylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.25-2.4 (m, 2H), 2.97 (s, 3H), 3.2-4.0 (m, 8H), 3.45 (m, 2H), 4.0 (s, 3H), 4.32 (m, 2H), 6.1 (s, 2H), 6.95-7.05 (m, 3H), 7.45 (s, 1H), 8.1 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 476.

[10] The reaction product was purified by column chromatography on reversed-phase silica using decreasingly polar mixtures of acetonitrile and a 1% solution of acetic acid in water. The product contained one equivalent of acetic acid and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.5-1.7 (m, 1H), 1.7-1.95 (m, 2H), 1.95-2.05 (m, 1H), 2.2-2.4 (m, 2H), 3.02 (m, 2H), 3.15-3.45 (m, 4H), 3.55 (d, 1H), 3.6 (m, 1H), 4.0 (s, 3H), 4.3 (m, 2H), 6.1 (s, 2H), 6.95-7.05 (m, 3H), 7.4 (s, 1H), 8.1 (s, 1H), 9.12 (s, 1H); Mass Spectrum: $M+H^+$ 477.

[11] The reaction product was purified by column chromatography on reversed-phase silica using decreasingly polar mixtures of acetonitrile and a 1% solution of acetic acid in water. The product contained 0.5 equivalents of acetic acid and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.1 (s, 3H), 2.35 (m, 2H), 2.9-3.1 (m, 2H), 3.2 (m, 1H), 3.3-3.5 (m, 3H), 3.65 (d, 2H), 4.05 (s, 3H), 4.07 (m, 1H), 4.35 (m, 2H), 4.55 (d, 1H), 6.12 (s, 2H), 7.0-7.1 (m, 3H), 7.5 (s, 1H), 8.15 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 504.

[12] The reaction product was purified by column chromatography on reversed-phase silica using decreasingly polar mixtures of acetonitrile and a 1% solution of acetic acid in water. The product contained 0.9 equivalents of acetic acid and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3-2.4 (m, 2H), 3.0 (s, 3H), 3.1-3.3 (m, 4H), 3.4 (m, 2H), 3.7 (d, 2H), 3.8 (d, 2H), 4.0 (s, 3H), 4.3 (m, 2H), 6.1 (s, 2H), 6.95-7.05 (m, 3H), 7.45 (s, 1H), 8.1 (s, 1H), 9.12 (s, 1H); Mass Spectrum: $M+H^+$ 540.

[[13] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.25-2.4 (m, 2H), 3.2-3.9 (m, 8H), 3.45 (m, 2H), 3.95 (d, 2H), 4.02 (s, 3H), 4.35 (m, 2H), 5.55-5.65 (m, 2H), 5.85-6.0 (m, 1H), 6.1 (s, 2H), 6.95-7.1 (m, 3H), 7.45 (s, 1H), 8.1 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 502.

[14] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline and N-methyl-N-prop-2-ynylamine and the reaction

mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: (DMSOd_6) 2.3 (m, 2H), 2.82 (s, 3H), 3.23-3.39 (m, 2H), 3.84 (m, 1H), 4.0 (s, 3H), 4.15 (d, 2H), 4.3 (t, 2H), 6.03 (s, 2H), 6.92-7.0 (m, 3H), 7.54 (s, 1H), 8.21 (s, 1H), 8.93 (s, 1H); Mass Spectrum: M+H^+ 445.

The 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxy anilino)quinoline used as a starting material was prepared as follows:-

Diisopropyl azodicarboxylate (0.29 g) was added dropwise to a stirred suspension of 3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.4 g), prepared as described in Example 4). 3-bromopropanol (0.25 g), triphenyl phosphine (0.44 g) and methylene chloride (15 ml). The mixture was stirred at ambient temperature for 18 hours. The mixture was evaporated and the residue was purified by column chromatography on silica eluting with increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. The gum so obtained was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.4 g); NMR Spectrum: (DMSOd_6) 2.32 (m, 2H), 3.68 (t, 2H), 3.94 (s, 3H), 4.26 (t, 2H), 5.98 (s, 2H), 6.8-6.92 (m, 3H), 7.32 (s, 1H), 7.78 (s, 1H), 8.42 (s, 1H); Mass Spectrum: M+H^+ 458.

[15] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours rather than being heated to 60°C. The product gave the following characterising data; NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 2.12 (s, 3H), 2.24–2.36 (m, 4H), 2.45–2.55 (m, 4H), 2.75 (t, 2H), 3.9 (s, 3H), 4.23 (t, 2H), 5.97 (s, 2H), 6.8-6.93 (m, 3H), 7.32 (s, 1H), 7.75 (s, 1H), 8.41 (s, 1H), 9.48 (s, 1H); Mass Spectrum: M+H^+ 462.

The 7-(2-bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylene dioxyanilino)quinoline used as a starting material was prepared using an analogous procedure to that described above for 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline. 3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was reacted with 2-bromoethanol to give the starting material in 82% yield; NMR Spectrum: (DMSOd_6) 3.88 (t, 2H), 3.94 (s, 3H), 4.51 (t, 2H), 5.96 (s, 2H), 6.8-6.93 (m, 3H), 7.34 (s, 1H), 7.8 (s, 1H), 8.42 (s, 1H), 9.53 (s, 1H); Mass Spectrum: M+H^+ 444.

[16] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.04 (s, 3H), 3.0-3.64 (m, 8H), 3.69 (m, 2H), 4.0 (s, 3H), 4.68 (m, 2H), 6.06 (s, 2H), 6.94-7.01 (m, 3H), 7.53 (s, 1H), 8.19 (s, 1H), 8.99 (s, 1H); Mass Spectrum: $M+H^+$ 477.

[17] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.3-3.82 (m, 12H), 4.02 (s, 3H), 4.61 (m, 2H), 5.48-5.6 (m, 2H), 5.9-6.03 (m, 1H), 6.04 (s, 2H), 6.93-7.0 (m, 3H), 7.58 (s, 1H), 8.28 (s, 1H), 8.98 (s, 1H); Mass Spectrum: $M+H^+$ 488.

[18] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.5 (m, 2H), 3.71 (m, 1H), 4.0 (s, 5H), 4.54 (m, 2H), 6.03 (s, 2H), 6.9-7.0 (m, 3H), 7.58 (s, 1H), 8.28 (s, 1H), 8.94 (s, 1H), 9.83 (br s, 1H); Mass Spectrum: $M+H^+$ 417.

[19] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.92 (s, 3H), 3.69 (m, 2H), 3.85 (m, 1H), 4.02 (s, 3H), 4.22 (d, 2H), 4.67 (t, 2H), 6.04 (s, 2H), 6.92-7.0 (m, 3H), 7.6 (s, 1H), 8.34 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 431.

[20] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.25 g), 3-fluoropyrrolidine hydrochloride (Synthetic Letters, 1995, 1, 55-57; 0.134 g) and N,N-diisopropyl-N-ethylamine (0.4 ml) in 2-methoxyethanol (5 ml) and the mixture was stirred and heated to 85°C for 24 hours. The product (0.1 g) gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.26 (t, 2H), 1.95-2.25 (m, 4H), 2.44-2.51 (m, 1H), 2.68-2.74 (m, 3H), 2.79-2.95 (m, 3H), 3.7 (s, 3H), 4.25 (t, 2H), 5.06-5.28 (m, 1H), 5.94 (s, 2H), 6.62-6.65 (m, 2H), 6.73(d, 1H), 6.83 (t, 1H), 6.97 (s, 1H), 7.37 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 465.

[21] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.25 g), 3,3-difluoropyrrolidine hydrochloride (Synthetic Letters, 1995, 1, 55-57; 0.1 g) and N,N-diisopropyl-N-ethylamine (0.4 ml) in 2-methoxyethanol (5 ml) and the mixture was stirred and heated to 85°C for 24 hours. The reaction product was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (4M) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt (0.16 g) and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.21-2.38 (m, 2H), 2.54-2.74 (m, 2H), 3.43 (t, 2H), 3.62-4.26 (m, 5H), 4.32 (t, 2H), 6.06 (s, 2H), 6.94-7.03 (m, 3H), 7.57 (s, 1H), 8.26 (s, 1H), 8.98 (s, 1H), 11.22 (br s, 1H), 11.83-12.58 (m, 1H); Mass Spectrum: $M+H^+$ 483.

[22] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.25 g), 4-fluoropiperidine hydrochloride (J. Org. Chem., 1979, 44, 771-777; 0.17 g) and N,N-diisopropyl-N-ethylamine (0.4 ml) in 2-methoxyethanol (5 ml) and the mixture was stirred and heated to 85°C for 24 hours. The product (0.13 g) gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.8-2.0 (m, 4H), 2.07-2.14 (m, 2H), 2.37-2.44 (m, 2H), 2.52-2.63 (m, 4H), 3.7 (s, 3H), 4.24 (t, 2H), 4.56-4.79 (m, 1H), 5.94 (s, 2H), 6.63 (d, 1H), 6.68 (s, 1H), 6.73 (d, 1H), 6.83 (t, 1H), 6.98 (s, 1H), 7.38 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 479.

[23] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.25 g), 4,4-difluoropiperidine (Tetrahedron, 1977, 33, 1707-1710; 0.154 g) and N,N-diisopropyl-N-ethylamine (0.4 ml) in 2-methoxyethanol (5 ml) and the mixture was stirred and heated to 85°C for 24 hours. The product (0.16 g) gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.93-2.17

(m, 6H), 2.54-2.62 (m, 6H), 3.7 (s, 3H), 4.24 (t, 2H), 5.94 (s, 2H), 6.6 (d, 1H), 6.69 (s, 1H), 6.73 (d, 1H), 6.83 (t, 1H), 6.98 (s, 1H), 7.38 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 497.

[24] The reactants were 7-(4-chlorobutoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline hydrochloride salt and 1-methylpiperazine. Moreover, 1-propanol was used in place of DMF and the reaction mixture was heated to 90°C for 18 hours. The reaction product was dissolved in ethyl acetate and a solution of hydrogen chloride in diethyl ether (4M, 1 ml) was added. The resultant solid was isolated and washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.9-1.95 (m, 4H), 2.81 (br s, 3H), 3.2-3.8 (m, 10H), 4.02 (s, 3H), 4.22 (br s, 2H), 6.04 (s, 2H), 6.93-7.01 (m, 3H), 7.59 (s, 1H), 8.26 (s, 1H), 8.97 (s, 1H), 11.28 (br s, 1H); Mass Spectrum: $M+H^+$ 490.

The 7-(4-chlorobutoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline hydrochloride salt used as a starting material was prepared as follows :-

A mixture of 4-chloro-7-(4-chlorobutoxy)-3-cyano-6-methoxyquinoline (J. Medicinal Chemistry, 2001, 44, 3965-3977; 1.0 g), 2,3-methylenedioxyaniline (0.46 g) and 1-propanol (25 ml) was stirred and heated to 100°C for 5 hours. The mixture was allowed to cool to ambient temperature and the precipitate was isolated and washed in turn with cold 1-propanol (25 ml) and diethyl ether (2 x 25 ml). The solid was dried under vacuum. There was thus obtained the required starting material (1.3 g); NMR Spectrum: ($DMSOd_6$) 1.9-1.98 (m, 4H), 3.74 (t, 2H), 4.23 (t, 2H), 6.04 (s, 2H), 6.94-7.01 (m, 3H), 7.5 (s, 1H), 8.18 (s, 1H), 8.96 (s, 1H), 11.11 (br s, 1H).

[25] The reactants were 7-(4-chlorobutoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline hydrochloride salt and 1-acetylpiperazine. Moreover, 1-propanol was used in place of DMF and the reaction mixture was heated to 90°C for 18 hours. The reaction product was dissolved in ethyl acetate and a solution of hydrogen chloride in diethyl ether (1M, 1 ml) was added. The resultant solid was isolated and washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.88-1.95 (m, 4H), 2.03 (s, 3H), 2.8-3.22 (m, 5H), 3.4-3.64 (m, 3H), 3.91-4.06 (m, 4H), 4.22 (br s, 2H), 4.37-4.42 (m, 1H), 6.05 (s, 2H), 6.92-7.02 (m, 3H), 7.62 (s, 1H), 8.31 (s, 1H), 9.01 (s, 1H), 11.21 (br s, 1H), 11.43 (br s, 1H); Mass Spectrum: $M+H^+$ 518.

[26] 1,2,3,6-Tetrahydropyridine was used as the heterocycle reactant. Moreover, 2-methoxyethanol was used in place of DMF and the reaction mixture was heated to 90°C for 5 hours. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.97 (m, 2H), 2.08 (s, 2H), 2.55 (m, 4H), 2.95 (s, 2H), 3.95 (s, 3H), 4.21 (t, 2H), 5.68 (m, 2H), 5.99 (s, 2H), 6.87 (m, 2H), 6.92 (t, 1H), 7.32 (s, 1H), 7.78 (s, 1H), 8.42 (s, 1H), 9.49 (s, 1H); Mass Spectrum: $M+H^+$ 459.

[27] 2-Methoxyethanol was used in place of DMF and the reaction mixture was heated to 100°C for 2 hours. The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.74 (m, 2H), 1.95 (m, 2H), 2.18 (m, 2H), 2.48 (t, 2H), 2.56 (t, 2H), 2.97 (t, 2H), 3.7 (s, 3H), 4.18 (t, 2H), 5.66 (m, 1H), 5.75 (m, 1H), 5.93 (s, 2H), 6.64 (d, 1H), 6.73 (d, 1H), 6.82 (t, 1H), 6.9 (s, 1H), 7.02 (s, 1H), 7.33 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 473.

[28] 2,5-Dimethylpyrrole was used as the heterocycle reactant. Moreover, 2-methoxyethanol was used in place of DMF and the reaction mixture was heated to 95°C for 12 hours. The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.16-2.32 (m, 2H), 2.23 (s, 6H), 3.72 (s, 3H), 4.04 (t, 2H), 4.14 (t , 2H), 5.77 (s, 2H), 5.95 (s, 2H), 6.63 (m, 2H), 6.76 (d ,1H), 6.86 (t, 1H), 6.98 (s, 1H), 7.33 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 471.

[29] 2,5-Dimethyl-3-pyrroline was used as the heterocycle reactant, the material being obtained commercially as a mixture of cis and trans isomers based on the stereochemical relationship of the methyl groups. 2-Methoxyethanol was used in place of DMF and the reaction mixture was heated to 95°C for 12 hours. Two isomeric products were obtained, based on the stereochemical relationship of the methyl groups. The isomers were separated during the chromatographic purification step and gave the following characterising data;
Isomer 1: NMR Spectrum: ($CDCl_3$) 1.16 (d, 6H), 2.08-2.18 (m, 2H), 2.91 (t, 2H), 3.61 (m, 2H), 3.72 (s, 3H), 4.27 (t, 2H), 5.55 (s, 2H), 5.92 (s, 2H), 6.63 (m, 2H), 6.73 (d, 1H), 6.86 (t, 1H), 6.98 (s, 1H), 7.39 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M-H^-$ 471.
Isomer 2: NMR Spectrum: ($CDCl_3$) 1.16 (br s, 6H), 2.08-2.13 (br s, 2H), 2.91 (br s, 2H), 3.72 (s, 3H), 3.9 (br s, 2H), 4.27 (m, 2H), 5.72 (s, 2H), 5.95 (s, 2H), 6.62-6.88 (m, 4H), 7.02 (s, 1H), 7.38 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M-H^-$ 471.

[30] The reactants were 7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline and 1,2,3,6-tetrahydropyridine. Moreover, 2-methoxyethanol was used in place of DMF and the reaction mixture was heated to 100°C

for 12 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M solution of ammonia in methanol as eluent. The material so obtained was dissolved in ethyl acetate and a solution of hydrogen chloride in diethyl ether (1M, 1 ml) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.18-3.96 (m, 8H), 4.05 (s, 3H), 4.46-4.63 (m, 2H), 5.68-6.0 (m, 3H), 6.07 (s, 2H), 6.92-7.02 (m, 3H), 7.62 (s, 1H), 8.33 (s, 1H), 8.97 (s, 1H), 11.28 (br s, 2H); Mass Spectrum: $M+H^+$ 477.

The 7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline used as a starting material was prepared as follows :-

Carbon tetrachloride (0.26 ml) was added to a mixture of (2S)-3-benzyloxy-2-fluoropropan-1-ol (J. Org. Chem., 1997, 62, 7546-7547; 0.44 g), triphenylphosphine (0.69 g) and methylene chloride (10 ml) and the mixture was stirred at ambient temperature for 12 hours. A further portion of triphenylphosphine (0.3 g) was added and the mixture was stirred at ambient temperature for 5 hours. The mixture was purified by column chromatography on silica using a 9:1 mixture of hexane and ethyl acetate as eluent. There was thus obtained (2R)-3-benzyloxy-2-fluoropropyl chloride as an oil (0.4 g); NMR Spectrum: ($CDCl_3$) 3.66-3.81 (m, 4H), 4.55-4.62 (m, 2H), 4.71-4.87 (m, 1H), 7.28-7.38 (m, 5H).

A solution of (2R)-3-benzyloxy-2-fluoropropyl chloride (0.65 g) in methylene chloride (15 ml) was cooled to –78°C and boron trichloride (1M solution in methylene chloride; 4.8 ml) was added. The mixture was stirred at –78°C for 3 hours. The mixture was poured into a 1N aqueous hydrochloric acid solution (50 ml) and extracted with methylene chloride. The organic phase was dried over magnesium sulphate and concentrated by evaporation to a volume of approximately 20 ml. There was thus obtained a solution of (2R)-3-chloro-2-fluoropropan-1-ol which was used without further purification.

Triphenylphosphine (1 g) and 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (0.83 g) were added in turn to the solution of (2R)-3-chloro-2-fluoropropan-1-ol in methylene chloride. Diisopropyl azodicarboxylate (0.6 ml) was added and the mixture was stirred at ambient temperature for 12 hours. The mixture was poured into water and the organic layer was separated, washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated. The crude product so obtained was purified by column chromatography on silica using a 1:1 mixture of isohexane and ethyl acetate as eluent. There

was thus obtained 4-chloro-7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxyquinoline (0.66 g); NMR Spectrum: ($DMSOd_6$) 4.02 (s, 3H), 3.9-4.12 (m, 2H), 4.42-4.64 (m, 2H), 5.09-5.31 (m, 1H), 7.47 (s, 1H), 7.6 (s, 1H), 8.44 (br s, 1H), 8.98 (s, 1H).

A mixture of 4-chloro-7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxyquinoline (0.27 g), 2,3-methylenedioxyaniline (0.13 g) and 1-propanol was stirred and heated to 90°C for 18 hours. The mixture was allowed to cool to ambient temperature. The precipitate was isolated and washed in turn with cold 1-propanol (10 ml) and with diethyl ether (2 x 10 ml). There was thus obtained 7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.26 g); NMR Spectrum: ($DMSOd_6$) 4.01 (s, 3H), 3.93-4.14 (m, 2H), 4.38-4.58 (m, 2H), 5.14-5.32 (m, 1H), 6.05 (s, 2H), 6.92-7.01 (m, 3H), 7.52 (s, 1H), 8.2 (s, 1H), 8.95 (s, 1H), 11.09 (br s, 1H); Mass Spectrum: $M+H^+$ 430.

[31] The reactants were 7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline and morpholine. Moreover, 2-methoxyethanol was used in place of DMF and the reaction mixture was heated to 100°C for 12 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M solution of ammonia in methanol as eluent. The material so obtained was dissolved in ethyl acetate and a solution of hydrogen chloride in diethyl ether (1M, 1 ml) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.25-3.37 (m, 4H), 3.52-3.72 (m, 2H), 3.89-3.97 (m, 4H), 4.02 (s, 3H), 4.40-4.65 (m, 2H), 5.55-5.81 (m, 1H), 6.0 (s, 2H), 6.88-6.96 (m, 3H), 7.59 (s, 1H), 8.15 (s, 1H), 8.69 (s, 1H); Mass Spectrum: $M+H^+$ 481.

[32] The reactants were 7-(3-chloropropoxy)-3-cyano-6-methoxy-4-[4-(2-methoxyethyl)-2,3-methylenedioxyanilino]quinoline and morpholine. The reaction product was treated with a 1M solution of hydrogen chloride in diethyl ether. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; Mass Spectrum: $M-H^-$ 519.

7-(3-chloropropoxy)-3-cyano-6-methoxy-4-[4-(2-methoxyethyl)-2,3-methylenedioxyanilino]quinoline was prepared by reacting 4-chloro-(3-chloropropoxy)-3-cyano-6-methoxyquinoline with 4-(2-methoxyethyl)-2,3-methylendioxyaniline. This gave a product with the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.25 (m, 2H), 2.78 (t, 2H), 3.25 (s, 3H), 3.54 (t, 2H), 3.81 (t, 2H), 3.93 (s, 3H), 4.28 (t, 2H), 5.97 (s, 2H),

6.78 (m, 2H), 7.33 (s, 1H), 7.77 (s, 1H), 8.39 (s, 1H), 9.42 (s, 1H); Mass Spectrum: $M+H^+$ 470.

The 4-(2-methoxyethyl)-2,3-methylendioxyaniline used as a starting ws prepared as described in Example 6(19).

Example 4

3-cyano-6-methoxy-7-(2-methoxyethoxy)-4-(2,3-methylenedioxyanilino)quinoline

A mixture of 3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.2 g), 2-bromoethyl methyl ether (0.09 g), potassium carbonate (0.22 g) and DMA (5 ml) was stirred and heated to 60°C for 3 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed in turn with water, a 2N aqueous sodium hydroxide solution and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. There was thus obtained the title compound solid as a mono-hydrochloride salt (0.135 g); NMR Spectrum: ($DMSOd_6$) 3.32 (s, 3H), 3.76 (m, 2H), 3.99 (s, 3H), 4.28 (m, 2H), 6.04 (s, 2H), 6.96 (m, 3H), 7.49 (s, 1H), 8.15 (s, 1H), 8.94 (s, 1H); Mass Spectrum: $M-H^-$ 392.

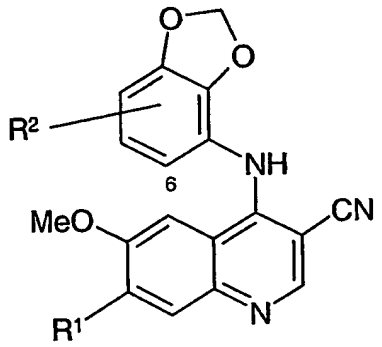
The 3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline used as a starting material was prepared as follows:-

A mixture of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (5 g), 2,3-methylenedioxyaniline (3.07 g) and propanol (100 ml) was stirred and heated to 115°C for 18 hours. The resultant precipitate was isolated, washed in turn with propanol and diethyl ether and dried under vacuum. There was thus obtained the title compound (5.51 g); NMR Spectrum: ($DMSOd_6$) 3.99 (s, 3H), 6.06 (s, 2H), 6.93-7.0 (m, 3H), 7.48 (s, 1H), 8.16 (s, 1H), 8.94 (s, 1H); Mass Spectrum: $M+H^+$ 336.

Example 5

Using an analogous procedure to that described in Example 4, the appropriate 3-cyano-7-hydroxyquinoline was reacted with the appropriate alkyl halide to give the compounds described in Table II.

Table II



Compound No. & Note	R^1	R^2
[1]	2-(2-hydroxyethoxy)ethoxy	hydrogen
[2]	2-hydroxyethoxy	hydrogen

Notes

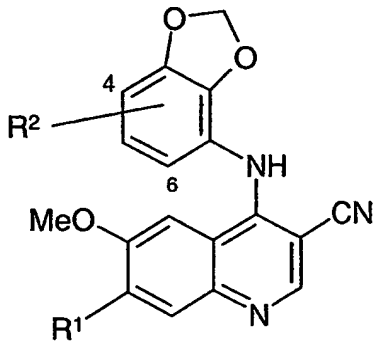
[1] 2-(2-Chloroethoxy)ethanol was used as the alkyl halide and the reaction mixture was heated to 60°C for 18 hours. However, unlike in Example 4, the product was not treated with a solution of hydrogen chloride in diethyl ether and, accordingly, the product was obtained as a free base. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.51 (m, 4H), 3.81 (m, 2H), 3.93 (s, 3H), 4.28 (m, 2H), 4.58 (m, 1H), 5.97 (s, 2H), 6.8-6.91 (m, 3H), 7.32 (s, 1H), 7.77 (s, 1H), 8.41 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 424.

[2] 2-Chloroethanol was used as the alkyl halide. The product was treated with a solution of hydrogen chloride in diethyl ether. The mono-hydrochloride salt so obtained gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.81 (t, 2H), 3.99 (s, 3H), 4.2 (t, 2H), 6.04 (s, 2H), 6.96 (m, 3H), 7.49 (s, 1H), 8.15 (s, 1H), 8.94 (s, 1H); Mass Spectrum: $M+H^+$ 380.

Example 6

Using an analogous procedure to that described in Example 1, the appropriate 4-chloro-3-cyanoquinoline was reacted with the appropriate 2,3-methylenedioxyaniline to give the compounds described in Table III. Unless otherwise stated, each product was obtained as a free base.

Table III



Compound No. & Note	R^1	R^2
[1]	methoxy	hydrogen
[2]	methoxy	6-chloro
[3]	methoxy	6-bromo
[4]	3-(4-methylpiperazin-1-yl)propoxy	6-fluoro
[5]	3-(4-methylpiperazin-1-yl)propoxy	5-bromo
[6]	3-(4-methylpiperazin-1-yl)propoxy	4-bromo
[7]	3-morpholinopropoxy	hydrogen
[8]	(2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propoxy	hydrogen
[9]	methoxy	4-iodo
[10]	methoxy	4-iodo-6-chloro
[11]	methoxy	4-bromo
[12]	methoxy	5-bromo
[13]	methoxy	5-fluoro
[14]	methoxy	4-hydroxymethyl
[15]	methoxy	4-methyl
[16]	methoxy	4-benzyl
[17]	methoxy	4-methylthio
[18]	3-(4-methylpiperazin-1-yl)propoxy	4-iodo
[19]	methoxy	4-(2-methoxyethyl)
[20]	3-(4-methylpiperazin-1-yl)propoxy	4-(2-methoxyethyl)

Compound No. & Note	R^1	R^2
[21]	3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy	4-(2-methoxyethyl)

Notes

[1] 4-Chloro-3-cyano-6,7-dimethoxyquinoline (International Patent Application WO 98/43960) was used as a starting material. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 4.02 (s, 3H), 4.05 (s, 3H), 6.12 (s, 2H), 7.0-7.1 (m, 3H), 7.45 (s, 1H), 8.12 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 350.

[2] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 4.04 (s, 3H), 4.06 (s, 3H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s,1H), 8.15 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 384 and 386.

[3] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 4.03 (s, 3H), 4.05 (s, 3H), 6.2 (s, 2H), 7.1 (d, 1H), 7.35 (d, 1H), 7.48 (s, 1H), 8.15 (s, 1H), 9.18 (s, 1H); Mass Spectrum: $M+H^+$ 428 and 430.

The 6-bromo-2,3-methylenedioxyaniline used as a starting material was prepared from 5-bromo-1,3-benzodioxole (Aldrich Chemical Company) using analogous procedures to those described in the portion of Example 1 above that is concerned with the preparation of 6-chloro-2,3-methylenedioxyaniline. There were thus obtained in turn :-

5-bromo-1,3-benzodioxole-4-carboxylic acid; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 6.15 (s, 2H), 6.95 (d, 1H), 7.1 (d, 1H); Mass Spectrum: $[M-H]^-$ 243;

tert-butyl N-(5-bromo-1,3-benzodioxol-4-yl)carbamate; NMR Spectrum: ($DMSOd_6$) 1.45 (s, 9H), 6.1 (s, 2H), 6.80 (d, 1H), 7.1 (d, 1H), 8.70 (s, 1H); and

6-bromo-2,3-methylenedioxyaniline; NMR Spectrum: ($DMSOd_6$) 5.05 (s, 2H), 6.0 (s, 2H), 6.25 (d, 1H), 6.9 (d, 1H); Mass Spectrum: $M+H^+$ 216 and 218.

[4] The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.12 (m, 2H), 2.85 (s, 3H),

3.27-3.88 (m, 10H), 4.0 (s, 3H), 4.32 (t, 2H), 6.11 (s, 2H), 6.87 (m, 1H), 7.0 (m, 1H), 7.52 (s, 1H), 8.16 (s, 1H), 8.97 (s, 1H); Mass Spectrum: $M+H^+$ 494.

The 6-fluoro-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of diisopropylamine (4.92 ml) and THF (100 ml) was cooled to -78°C and n-butyllithium (2.5 M in THF, 14 ml) was added dropwise. The mixture was stirred at -70°C for 30 minutes. 4-Fluoro-1,2-dimethoxybenzene (5 g) was added dropwise and the reaction mixture was stirred at -70°C for 20 minutes. Dry carbon dioxide gas was bubbled into the reaction mixture for 15 minutes. The resultant reaction mixture was allowed to warm to ambient temperature and was stirred for a further hour. Water was added and the organic solvent was evaporated. The residue was acidified to pH2 by the addition of 2N aqueous hydrochloric acid solution and the mixture was extracted with a mixture of diethyl ether and ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated. The solid so obtained was washed with pentane and dried under vacuum. There was thus obtained 6-fluoro-2,3-dimethoxybenzoic acid (3.4 g); NMR Spectrum: ($DMSOd_6$) 3.8 (s, 3H), 3.85 (s, 3H), 7.0 (t, 1H), 7.15 (m, 1H).

A mixture of 6-fluoro-2,3-dimethoxybenzoic acid (14 g), concentrated aqueous hydrobromic acid (47%, 230 ml) and acetic acid (200 ml) was stirred and heated to 140°C for 1 hour. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated to give 6-fluoro-2,3-dihydroxybenzoic acid (9.3 g); NMR Spectrum: ($DMSOd_6$) 6.55 (t, 1H), 6.9 (m, 1H), 9.3 (br s, 2H).

Thionyl chloride (6 ml) was added dropwise to a solution of 6-fluoro-2,3-dihydroxybenzoic acid (9.3 g) in methanol (80 ml) that had been cooled to 0°C. The resultant mixture was stirred and heated to 60°C for 24 hours. The mixture was evaporated and the residue was partitionned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica eluting with increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained methyl 6-fluoro-2,3-dihydroxybenzoate (7.2 g); NMR Spectrum: ($CDCl_3$) 4.0 (s, 3H), 5.45 (s, 1H), 6.5 (t, 1H), 7.0 (m, 1H).

Potassium fluoride (11.2 g) was added to a solution of methyl 6-fluoro-2,3-dihydroxybenzoate (7.2 g) in DMF (110 ml) and the mixture was stirred and heated to 100°C for 15 minutes. Diiodomethane (3.43 ml) was added and the mixture was stirred and heated to 100°C for 75 mnutes. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. The resultant residue was purified by colum chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained methyl 6-fluoro-2,3-methylenedioxybenzoate (4.5 g); NMR Spectrum: ($DMSOd_6$) 3.85 (s, 3H), 6.2 (s, 2H), 6.8 (m, 1H), 7.15 (m, 1H).

A suspension of the material so obtained, a 2N aqueous potassium hydroxide solution (23 ml) and methanol (60 ml) was stirred at ambient temperature for 3 hours. The mixture was evaporated and the residue was dissolved in water and the solution was acidified to pH2 by the addition of 6N aqueous hydrochloric acid. The resultant precipitate was isolated, washed with water and dried overnight under vacuum over phosphorus pentoxide. There was thus obtained 6-fluoro-2,3-methylenedioxybenzoic acid (4 g); NMR Spectrum: ($DMSOd_6$) 6.15 (s, 2H), 6.75 (m, 1H), 7.05 (m, 1H).

The material so obtained was dissolved in 1,4-dioxane (60 ml) and anhydrous tert-butanol (17 ml), diphenylphosphoryl azide (5 ml) and triethylamine (3.8 ml) were added in turn. The resultant mixture was stirred and heated to 100°C for 4.5 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the resultant residue was partitioned between ethyl acetate and a 5% aqueous citric acid solution. The organic phase was washed in turn with water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained tert-butyl N-(5-fluoro-1,3-benzodioxol-4-yl)carbamate (4.5 g); NMR Spectrum: ($CDCl_3$) 1.5 (s, 9H), 5.95 (br s, 1H), 6.0 (s, 2H), 6.55 (m, 2H).

A mixture of a portion (2.5 g) of the material so obtained, trifluoroacetic acid (15 ml) and methylene chloride (55 ml) was stirred at ambient temperature for 3.5 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 6-fluoro-2,3-

methylenedioxyaniline (1.1 g); NMR Spectrum: ($DMSOd_6$) 5.0 (br s, 2H), 5.95 (s, 2H), 6.15 (m, 1H), 6.55 (m, 1H).

[5] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.1 (m, 2H), 2.28 (s, 3H), 2.4-2.6 (m, 8H), 2.55 (t, 2H), 3.78 (s, 3H), 4.24 (t, 2H), 5.97 (s, 2H), 6.64 (s, 1H), 6.72 (s, 1H), 6.97 (s, 1H), 7.4 (s, 1H), 8.63 (s, 1H); Mass Spectrum: $M+H^+$ 554 and 556.

The 5-bromo-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 6-bromo-1,3-benzodioxole-4-carboxylic acid [Khim. Geterotsikl. Soedin 1979, 9, 1183-8 (Chemical Abstracts 92, 94280); 0.92 g], diphenylphosphoryl azide (1.08 g), tert-butanol (3 ml), triethylamine (0.34 g) and toluene (15 ml) were stirred and heated at 100°C for 4 hours. The resultant mixture was evaporated and the residue was partitioned between methyl tert-butyl ether and a 5% aqueous citric acid solution. The organic phase was washed with water and a saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated. The residual oil was purified by column chromatography on silica using a 5:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained tert-butyl N-(6-bromo-1,3-benzodioxol-4-yl)carbamate (0.6 g); NMR Spectrum: ($CDCl_3$) 1.52 (s, 9H), 5.95 (s, 2H), 6.39 (br s, 1H), 6.7 (d, 1H), 7.73 (br s, 1H).

A mixture of the material so obtained, trifluoroacetic acid (3 ml) and methylene chloride (8 ml) was stirred at ambient temperature for 1 hour. The solvent was evaporated and the residue was partitioned between methyl tert-butyl ether and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 4:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained 5-bromo-2,3-methylenedioxyaniline (0.318 g) as a colourless solid; NMR Spectrum: ($CDCl_3$) 3.6 (br s, 2H), 5.92 (s, 2H), 6.27 (m, 2H).

[6] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.15 (s, 3H), 2.25-2.5 (m, 10H), 3.94 (s, 3H), 4.18 (t, 2H), 6.09 (s, 2H), 6.84 (d, 1H), 7.09 (d, 1H), 7.3 (s, 1H), 7.74 (s, 1H), 8.43 (s, 1H), 9.52 (s, 1H); Mass Spectrum: $M+H^+$ 554 and 556.

[7] 4-Chloro-3-cyano-6-methoxy-7-(3-morpholinopropoxy)quinoline (International Patent Application WO 00/68201, page 52) was used as a starting material. The reaction product

was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.26–2.37 (m, 2H), 3.04–3.16 (m, 2H), 3.26–3.34 (t, 2H), 3.45–3.55 (m, 2H), 3.72–3.87 (m, 2H), 3.94–4.03 (m, 5H), 4.31 (t, 2H), 6.04 (s, 2H), 6.94–6.99 (m, 3H), 7.49 (s, 1H), 8.14 (s, 1H), 8.96 (s, 1H); Mass Spectrum: $M-H^-$ 461.

[8] The reaction mixture was stirred at 0°C for 2 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M solution of ammonia in methanol as eluent. The material so obtained was dissolved in ethyl acetate and a solution of hydrogen chloride in diethyl ether (1M, 1 ml) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.81 (s, 3H), 3.0-3.63 (m, 10H), 4.05 (s, 3H), 4.42-4.57 (m, 2H), 5.39-5.52 (m, 1H), 6.08 (s, 2H), 6.96-7.1 (m, 3H), 7.61 (s, 1H), 8.29 (s, 1H), 9.03 (s, 1H), 11.30 (br s, 1H); Mass Spectrum: $M+H^+$ 494.

The 4-chloro-3-cyano-7-[(2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propoxy]-6-methoxyquinoline used as a starting material was prepared as follows :-

A mixture of (2R)-3-benzyloxy-2-fluoropropyl chloride (0.4 g), 1-methylpiperazine (2.2 ml) and 2-methoxyethanol (5 ml) was stirred and heated to 80°C for 12 hours and then to 110°C for 6 hours. The resultant mixture was poured into a mixture of water (50 ml) and a saturated aqueous sodium chloride solution (50 ml) and extracted with ethyl acetate (3 x 25 ml). The organic extracts were dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7N solution of ammonia in methanol as eluent. There was thus obtained benzyl (2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propyl ether as an oil (0.27 g); NMR Spectrum: ($CDCl_3$) 2.28 (s, 3H), 2.33-2.75 (m, 10H), 3.61-3.68 (m, 2H), 4.58 (s, 2H), 4.73-4.91 (m, 1H), 7.28-7.38 (m, 5H).

The material so obtained was dissolved in methanol (10 ml) and 10% palladium-on-carbon (0.77 g) and ammonium formate (0.65 g) were added and the mixture was heated to reflux for 5 hours. A further portion of ammonium formate (0.7 g) was added and the mixture

was heated to reflux for 12 hours. The mixture was allowed to cool to ambient temperature and filtered. The filtrate was evaporated and the crude product so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7N solution of ammonia in methanol as eluent. There was thus obtained (2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propan-1-ol as an oil (0.082 g); NMR Spectrum: ($CDCl_3$) 2.28 (s, 3H), 2.3-2.71 (m, 8H), 2.74 (d, 1H), 2.79 (m, 1H), 3.84 (t, 1H), 3.89 (d, 1H), 4.59-4.75 (m, 1H); Mass Spectrum: $M+H^+$ 177.

Using an analogous procedure to that described in Example 3 for making 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline, (2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propan-1-ol (0.082 g) was reacted with 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (0.14 g) to give 4-chloro-3-cyano-7-[(2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propoxy]-6-methoxyquinoline.

[9] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.77 (s, 3H), 3.81 (s, 3H), 5.88 (s, 2H), 6.3 (d, 1H), 6.87 (d, 1H), 6.93 (s, 1H), 7.7 (s, 1H), 7.83 (s, 1H); Mass Spectrum: $M+H^+$ 476.

The 4-iodo-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

Benzyltrimethylammonium dichloroiodate (2.8 g) was added portionwise during 10 minutes to a stirred mixture of 2,3-methylenedioxyaniline (1 g), calcium carbonate (0.95 g), methanol (5 ml) and methylene chloride (10 ml). The reaction mixture was stirred at ambient temperature for 1.5 hours. The resultant mixture was diluted with water and extracted with methylene chloride. The organic phase was washed with water and with a saturated brine solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of isohexane and methylene chloride as eluent. There was thus obtained 4-iodo-2,3-methylenedioxyaniline as a solid (1.1 g); NMR Spectrum: ($DMSOd_6$) 5.04 (br s, 2H), 5.94 (s, 2H), 6.13 (d, 1H), 6.8 (d, 1H).

[10] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 4.0 (s, 6H), 6.18 (s, 2H), 7.38 (s, 1H), 7.48 (s, 1H), 7.88 (s, 1H), 8.44 (s, 1H), 9.45 (s, 1H); Mass Spectrum: $M+H^+$ 510.

The 6-chloro-4-iodo-2,3-methylenedioxyaniline used as a starting material was prepared by the reaction of 6-chloro-2,3-methylenedioxyaniline and

benzyltrimethylammonium dichloroiodate in an analogous manner to that described in Note [9] immediately above. The material so obtained gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 6.04 (s, 2H), 7.0 (s, 1H).

[11] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.96 (s, 3H), 3.97 (s, 3H), 6.08 (s, 2H), 6.83 (s, 1H), 7.08 (s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.43 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 428 and 430.

[12] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 3.83 (s, 3H), 4.05 (s, 3H), 5.98 (s, 2H), 6.76 (d, 1H), 6.84 (d, 1H), 6.9 (br s, 1H), 7.06 (s, 1H), 7.39 (s, 1H), 8.64 (s, 1H); Mass Spectrum: $M+H^+$ 428 and 430.

[13] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 3.81 (s, 3H), 4.05 (s, 3H), 5.96 (s, 2H), 6.3 (m, 1H), 6.5 (m, 1H), 6.64 (br s, 1H), 7.01 (s, 1H), 7.4 (s, 1H), 8.65 (s, 1H); Mass Spectrum: $M+H^+$ 368.

The 5-fluoro-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 5-bromo-2,3-methylenedioxyaniline (2.0 g), 1,2-bis(chlorodimethylsilyl)ethane (2.09 g), triethylamine (1.96 g) and methylene dichloride (50 ml) was stirred at ambient temperature for 88 hours. The resultant mixture was washed with a 5% aqueous sodium dihydrogen phosphate solution, dried over magnesium sulphate and evaporated. The oil so obtained was purified by column chromatography on neutral alumina using isohexane as eluent. There was thus obtained N-(5-bromo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine as an oil (2.4 g); NMR Spectrum: ($CDCl_3$) 0.13 (s, 12H), 0.86 (s, 4H), 5.87 (s, 2H), 6.59 (d, 1H), 6.67 (d, 1H).

n-Butyllithium (1.6M in THF, 1.1 ml) was added to a solution of N-(5-bromo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (0.6 g) in THF (10 ml) that had been cooled to -70°C and the mixture was stirred at -70°C for 1 hour. A solution of N-fluorobenzenesulphonimide (1.0 g) in THF (3 ml) was added and the mixture was allowed to warm to 0°C over 3 hours. The mixture was stirred at 0°C for a further hour. The mixture was poured into a cooled 1N aqueous hydrochloric acid solution and stirred for 5 minutes and extracted with diethyl ether. The aqueous phase was basified with a 40% aqueous sodium hydroxide solution and extracted with diethyl ether. The organic phase was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. There was thus

obtained 5-fluoro-2,3-methylenedioxyaniline as an oil (0.12 g) which was used without further purification.

[14] The reactants were 4-chloro-3-cyano-6,7-dimethoxyquinoline (0.082 g) and 4-tert-butyldimethylsilyloxymethyl-2,3-methylenedioxyaniline (0.1 g) and the initial product was 4-(4-tert-butyldimethylsilyloxymethyl-2,3-methylenedioxyanilino)-3-cyano-6,7-dimethoxyquinoline (0.115 g) which gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 0.1 (s, 6H), 0.94 (s, 9H), 3.71 (s, 3H), 4.03 (s, 3H), 4.72 (s, 2H), 5.95 (s, 2H), 6.63 (d, 1H), 6.7 (s, 1H), 6.94 (d, 1H), 6.99 (s, 1H), 7.38 (s, 1H), 8.62 (s, 1H); Mass Spectrum: $M+H^+$ 494. A solution of that material (0.38 g) in THF (6 ml) was treated with tetra-n-butylammonium fluoride (1M solution in THF; 1.5 ml) at ambient temperature for 5 hours. The reaction mixture was partitioned between ethyl acetate and a saturated aqueous ammonium chloride solution. The organic layer was separated, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. The product so obtained was trituated under diethyl ether. There was thus obtained the required product as a solid (0.197 g); NMR Spectrum: ($DMSOd_6$) 3.92 (d, 6H), 4.48 (d, 2H), 5.2 (t, 1H), 5.98 (s, 2H), 6.83 (d, 1H), 6.95 (d, 1H), 7.3 (s, 1H), 7.78 (s, 1H), 8.41 (s, 1H), 9.48 (s, 1H); Mass Spectrum: $M+H^+$ 380.

The 4-tert-butyldimethylsilyloxymethyl-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 2,3-dihydroxy-4-nitrobenzaldehyde (J. Med. Chem., 1992, 35, 4584-4588; 7.4 g), bromochloromethane (12.7 ml), caesium carbonate (25.4 g) and DMF (95 ml) was stirred and heated to 110°C for 3 hours. A further portion of bromochloromethane (6.0 ml) was added and the mixture was further heated to 110°C for 3 hours. A third portion of bromochloromethane (3.0 ml) was added and the mixture was further heated to 110°C for 1 hour. The mixture was poured into 2N aqueous hydrochloric acid solution (500 ml) and stirred for 15 minutes. Ethyl acetate (500 ml) was added and the mixture was filtered. The organic layer was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica using a 1:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained 2,3-methylenedioxy-4-nitrobenzaldehyde as a yellow solid (5.3 g); NMR Spectrum: ($DMSOd_6$) 6.49 (s, 2H), 7.37 (d, 1H), 7.64 (d, 1H), 10.10 (br s, 1H).

Sodium borohydride (0.75 g) was added portionwise to an ice-cooled mixture of 2,3-methylenedioxy-4-nitrobenzaldehyde (1.3 g) in methanol (35 ml) and the resultant mixture was stirred for 2 hours and allowed to warm to ambient temperature. The mixture was partitioned between ethyl acetate and a 2N aqueous hydrochloric acid solution. The organic layer was dried over magnesium sulphate and evaporated. There was thus obtained 2,3-methylenedioxy-4-nitrobenzyl alcohol as a solid (0.93 g); NMR Spectrum: ($CDCl_3$) 4.67 (d, 2H), 5.43 (t, 1H), 6.18 (s, 2H), 6.96 (d, 1H), 7.57 (d, 1H).

tert-Butyldimethylsilyl chloride (0.462 g) was added to a mixture of 2,3-methylenedioxy-4-nitrobenzyl alcohol (0.55 g), triethylamine (0.47 g), N,N-dimethylaminopyridine (0.01 g) and DMF (5 ml) and the mixture was stirred at ambient temperature for 2 hours. The resultant mixture was evaporated and the residue was partitioned between ethyl acetate and a dilute aqueous citric acid solution. The organic layer was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained tert-butyldimethylsilyl 2,3-methylenedioxy-4-nitrobenzyl ether as a solid (0.68 g); NMR Spectrum: ($CDCl_3$) 0.1 (s, 6H), 0.95 (s, 9H), 4.74 (s, 2H), 6.22 (s, 2H), 7.08 (d, 1H), 7.62 (d, 1H).

The material so obtained was added to a stirred mixture of hydrazine hydrate (0.36 ml). Raney nickel (50% dispersion in water; 0.18 g) and methanol (24 ml) and the reaction mixture was stirred at ambient temperature for 0.5 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained 4-tert-butyldimethylsilyloxymethyl-2,3-methylenedioxyaniline as an oil (0.56 g); NMR Spectrum: ($CDCl_3$) 0.1 (s, 6H), 0.92 (s, 9H), 3.52 (br s, 2H), 4.62 (s, 2H), 5.92 (s, 2H), 6.31 (d, 1H), 6.73 (d, 1H).

[15] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.93 (2 s, 6H), 5.97 (s, 2H), 6.76 (s, 2H), 7.3 (s, 1H), 7.78 (s, 1H), 8.4 (s, 1H), 9.44 (s, 1H); Mass Spectrum: $M+H^+$ 364.

The 4-methyl-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 2,3-methylenedioxy-4-nitrobenzyl alcohol (0.35 g), isopropyl isocyanate (2 ml), toluene (2 ml) and acetonitrile (2 ml) was heated to 70°C for 12 hours. The mixture

was evaporated and the residue was triturated under hexane. There was thus obtained2,3-methylenedioxy-4-nitrobenzyl N-isopropylcarbamate as a solid (0.37 g); NMR Spectrum: ($CDCl_3$) 1.18 (d, 6H), 3.83 (m, 1H), 4.6 (br s, 1H), 5.12 (s, 2H), 6.25 (s, 2H), 6.95 (d, 1H), 7.59 (d, 1H).

A mixture of a portion (0.2 g) of the material so obtained, 10% palladium-on-carbon catalyst (0.05 g) and ethyl acetate (5 ml) was stirred under an atmosphere pressure of hydrogen for 12 hours. The mixture was filtered and the filtrate was evaporated. There was thus obtained 4-methyl-2,3-methylenedioxyaniline as an oil (0.089 g); NMR Spectrum: ($CDCl_3$) 2.13 (s, 3H), 3.45 (br s, 2H), 5.91 (s, 2H), 6.23 (d, 1H), 6.51 (d, 1H).

[16] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 3.52 (s, 3H), 3.93 (s, 2H), 4.0 (s, 3H), 5.93 (s, 2H), 6.6 (d, 1H), 6.66 (s, 1H), 6.67 (d, 1H), 6.9 (s, 1H), 7.28-7.3 (m, 5H), 7.34 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 440.

The 4-benzyl-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 4-iodo-2,3-methylenedioxyaniline (3.0 g), 1,2-bis(chlorodimethylsilyl)ethane (2.57 g), triethylamine (2.33 g) and methylene dichloride (60 ml) was stirred at ambient temperature for 88 hours. The resultant mixture was evaporated. Isohexane was added to the residue and the mixture was filtered. The filtrate was evaporated and the resultant residue was purified by column chromatography on neutral alumina using isohexane as eluent. There was thus obtained N-(4-iodo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine as a solid (2.85 g); NMR Spectrum: ($CDCl_3$) 0.1 (s, 12H), 0.82 (s, 4H), 5.9 (s, 2H), 6.26 (d, 1H), 6.98 (d, 1H).

n-Butyllithium (1.6M in THF, 1.35 ml) was added to a solution of N-(4-iodo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (0.8 g) in THF (12 ml) that had been cooled to -70°C and the mixture was stirred at -70°C for 30 minutes. Benzaldehyde (0.23 g) was added and the mixture was stirred at -70°C for 2 hours and then allowed to warm to 0°C. The resultant mixture was poured into a cooled 1N aqueous hydrochloric acid solution and stirred for 5 minutes and extracted with diethyl ether. The aqueous phase was basified with a 40% aqueous sodium hydroxide solution and extracted with diethyl ether. The organic phase was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica using a 1:4 mixture of isohexane and tert-butyl methyl ether as

eluent. There was thus obtained 4-(α-hydroxybenzyl)-2,3-methylenedioxyaniline as an oil (0.213 g); NMR Spectrum: ($CDCl_3$) 2.4 (s, 1H), 3.54 (br s, 2H), 5.9 (s, 1H), 5.92 (s, 2H), 6.26 (d, 1H), 6.6 (d, 1H), 7.25 (m, 1H), 7.32 (t, 2H), 7.4 (d, 2H).

A mixture of the material so obtained, 10% palladium-on-carbon catalyst (0.02 g) and ethanol (10 ml) was stirred at ambient temperature under an atmosphere pressure of hydrogen for 12 hours. The mixture was filtered and the residue was evaporated. There was thus obtained 4-benzyl-2,3-methylenedioxyaniline as a colourless oil (0.137 g); Mass Spectrum: $M+H^+$ 228.

[17] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.48 (s, 3H), 3.75 (s, 3H), 4.03 (s, 3H), 6.0 (s, 2H), 6.61 (d, 1H), 6.66 (br s, 1H), 6.82 (d, 1H), 6.98 (s, 1H), 7.38 (s, 1H), 8.62 (s, 1H); Mass Spectrum: $M+H^+$ 396.

The 4-methylthio-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

n-Butyllithium (1.6M in hexane, 1.28 ml) was added during 10 minutes to a solution of N-(4-iodo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (0.75 g) in THF (25 ml) that had been cooled to -78°C and the mixture was stirred at -78°C for 25 minutes. Dimethyl disulphide (0.288 g) was added and the mixture was stirred at –78°C for 3 hours. The resultant mixture was allowed to warm to 0°C. A 1N aqueous hydrochloric acid solution (25 ml) was added and the mixture was stirred for 10 minutes. The mixture was washed with diethyl ether. The aqueous phase was basified to pH11 by the addition of a concentrated aqueous sodium hydroxide solution and extracted with methylene chloride. The organic extract was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on reverse-phase silica using a decreasingly polar gradient of acetonitrile in water (plus 0.1% trifluoroacetic acid) as eluent. There was thus obtained 4-methylthio-2,3-methylenedioxyaniline as an oil which crystallized on standing (0.13 g); NMR Spectrum: ($CDCl_3$) 2.38 (s, 3H), 3.59 (br s, 2H), 5.98 (s, 2H), 6.27 (d, 1H), 6.74 (d, 1H).

[18] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.18 (s, 3H), 2.25-2.5 (m, 10H), 3.94 (s, 3H), 4.22 (t, 2H), 6.11 (s, 2H), 6.76 (d, 1H), 7.22 (d, 1H), 7.35 (s, 1H), 7.75 (s, 1H), 8.48 (s, 1H), 9.54 (s, 1H); Mass Spectrum: $M-H^-$ 600.

The 4-chloro-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline used as a starting material was prepared as follows :-

A solution of diisopropyl azodicarboxylate (12.1 ml) in methylenechloride (50 ml) was added dropwise during 30 minutes to a stirred mixture of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (12 g), 1-(3-hydroxypropyl)-4-methylpiperazine (9.7 g), triphenylphosphine (16.1 g) and methylenedichloride (200 ml) that had been cooled to 5°C. The resultant mixture was allowed to warm to ambient temperature and was then stirred for 1 hour. Further portions of diisopropyl azodicarboxylate (1.2 ml) and triphenylphosphine (1.6 g) were added and the mixture was stirred at ambient temperature for a further 1 hour. The mixture was poured into water and the organic layer was separated, washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained the required starting material as a solid (14.5 g); NMR Spectrum: ($DMSOd_6$) 1.95 (m, 2H), 2.13 (s, 3H), 2.24-2.5 (m, 10H), 4.0 (s, 3H), 4.25 (t, 2H), 7.43 (s, 1H), 7.51 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 375 and 377.

[19] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.88 (m, 2H), 3.37 (s, 3H), 3.62 (t, 2H), 3.72 (s, 3H), 4.03 (s, 3H), 5.93 (s, 2H), 6.64 (d, 1H), 6.68 (s, 1H), 6.76 (d, 1H), 6.95 (s, 1H), 7.37 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 408.

The 4-(2-methoxyethyl)-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

Potassium tert-butoxide (1M solution in THF; 1.35 ml) was added to a mixture of methoxymethyltriphenylphosphonium chloride (0.42 g) and THF (3 ml) and the resultant mixture was stirred at ambient temperature for 0.5 hours. A solution of 2,3-methylenedioxy-4-nitrobenzaldehyde (0.12 g) in THF (2 ml) was added and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was diluted with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-(2-methoxyethenyl)-2,3-methylenedioxy-1-nitrobenzene as a solid (0.108 g) in the form of a 2.7:1 mixture of Z and E isomers; NMR Spectrum: ($CDCl_3$) 3.77 (s, 3H), 5.72 (d, 1H), 6.24 (s, 2H), 6.74 (d, 1H), 7.48 (d, 1H), 7.56 (d, 1H).

A mixture of the material so obtained, 10% palladium-on-carbon (0.02 g) and ethyl acetate (4 ml) was stirred under an atmosphere pressure of hydrogen at ambient temperature

for 12 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained 4-(2-methoxyethyl)-2,3-methylenedioxyaniline as an oil (0.05 g); NMR Spectrum: ($CDCl_3$) 2.78 (t, 2H), 3.36 (s, 3H), 3.48 (br s, 2H), 3.57 (t, 2H), 5.92 (s, 2H), 6.27 (d, 1H), 6.54 (d, 1H).

[20] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.15 (s, 3H), 2.4-2.72 (m, 10H), 2.79 (t, 2H), 3.22 (s, 3H), 3.51 (t, 2H), 3.91 (s, 3H), 4.19 (t, 2H), 5.98 (s, 2H), 6.79 (m, 2H), 7.3 (s, 1H), 7.74 (s, 1H), 8.4 (s, 1H), 9.45 (s, 1H); Mass Spectrum: $M-H^-$ 532.

[21] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.98 (m, 2H), 2.68 (t, 2H), 2.83 (t, 2H), 2.93 (br s, 4H), 3.1 (br s, 4H), 3.28 (s, 3H), 3.57 (t, 2H), 3.96 (s, 3H), 4.03 (t, 2H), 5.99 (s, 2H), 6.81 (m, 2H), 7.36 (s, 1H), 7.78 (s, 1H), 8.43 (s, 1H), 9.45 (s, 1H); Mass Spectrum: $M+H^+$ 569.

The 4-chloro-3-cyano-7-[3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy]-6-methoxyquinoline used as a starting material was prepared as follows :-

A mixture of 3-aminopropan-1-ol (0.65 ml) and divinyl sulphone (1 g) was heated to 110°C for 45 minutes. The mixture was allowed to cool to ambient temperature and was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 4-(3-hydroxypropyl)-1,1-dioxotetrahydro-4H-thiazine (0.8 g); NMR Spectrum: ($CDCl_3$) 1.7-1.8 (m, 2H), 2.73 (t, 2H), 3.06 (br s, 8H), 3.25 (s, 1H), 3.78 (t, 2H); Mass Spectrum: $M+H^+$ 194.

Diethyl azodicarboxylate (1.72 g) was added dropwise to a suspension of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (1 g), 4-(3-hydroxypropyl)-1,1-dioxotetrahydro-4H-thiazine (1.23 g), triphenyl phosphine (1.45 g) and methylene chloride (10 ml) and the mixture was stirred at ambient temperature for 16 hours. The resultant mixture was washed with water and with a saturated brine solution. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride, ethyl acetate and a saturated methanolic ammonia solution as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained 4-chloro-3-cyano-7-[3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy]-6-methoxyquinoline (0.15 g); NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.64 (t,

2H), 2.88–2.93 (m, 4H), 3.07–3.12 (m, 4H), 4.0 (s, 3H), 4.29 (t, 2H), 7.44 (s, 1H), 7.55 (s, 1H), 8.96 (s, 1H); Mass Spectrum: $M+H^+$ 410.

Example 7

3-cyano-7-[(2R)-2-hydroxy-3-morpholinopropoxy]-6-methoxy-4-(2,3-methylene dioxyanilino)quinoline

A mixture of 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.1 g), morpholine (0.11 g) and propanol (5 ml) was stirred and heated to 80°C for 3 hours. The resultant mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether to give the title compound (0.04 g); NMR Spectrum: ($DMSOd_6$) 2.35-2.52 (m, 6H), 3.56 (m, 4H), 3.93 (s, 3H), 4.0-4.1 (m, 2H), 4.17 (m, 1H), 4.9 (d, 1H), 5.98 (s, 2H), 6.9-6.92 (m, 3H), 7.33 (s, 1H), 7.86 (s, 1H), 8.4 (s, 1H), 9.48 (br s, 1H); Mass Spectrum: $M-H^-$ 477.

The 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline used as a starting material was prepared as follows :-

(2R)-(-)-Glycidyl tosylate (0.52 g) was added to a mixture of 3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.67 g), potassium carbonate (0.87 g) and DMA (15 ml) and the mixture was stirred and heated to 60°C for 3 hours. The resultant mixture was evaporated and the residue was partitioned between methylene chloride and water. The organic phase was washed with water and with a saturated brine solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline as a solid (0.3 g); NMR Spectrum: ($DMSOd_6$) 2.75 (m, 1H), 2.88 (m, 1H), 3.4 (m, 1H), 3.95 (s, 3H), 3.95-4.01 (m, 1H), 4.53 (m, 1H), 5.98 (s, 2H), 6.8-6.92 (m, 3H), 7.33 (s, 1H), 7.79 (s, 1H), 8.41 (s, 1H), 9.51 (s, 1H); Mass Spectrum: $M+H^+$ 392.

Example 8

7-[(2R)-3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline

Using an analogous procedure to that described in Example 7, 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was reacted with 1-acetylpiperazine to give the title compound in 35% yield; NMR Spectrum: ($DMSOd_6$) 1.96 (s, 3H), 2.34-2.54 (m, 6H), 3.35-3.45 (m, 4H), 3.94 (s, 3H), 4.0-4.1 (m, 2H), 4.13-4.21 (m, 1H), 4.94 (d, 1H), 5.97 (s, 2H), 6.80-6.92 (m, 3H), 7.23 (s, 1H), 7.76 (s, 1H), 8.4 (s, 1H), 9.49 (s, 1H); Mass Spectrum: $M+H^+$ 520.

Example 9

3-cyano-7-[(2R)-2-hydroxy-3-methoxypropoxy]-6-methoxy-4-(2,3-methylene dioxyanilino)quinoline

A mixture of 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.1 g), a methanolic sodium methoxide solution (25%, 1 ml) and methanol (5 ml) was stirred at ambient temperature for 18 hours. The mixture was evaporated and the residue was dissolved in methylene chloride and washed with water and with a saturated brine solution and dried over magnesium sulphate. The organic phase was evaporated and the residue was was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The resultant gum was triturated under diethyl ether to give the title compound as a solid (0.035 g); NMR Spectrum: ($DMSOd_6$) 3.29 (s, 3H), 3.32-3.49 (m, 2H), 3.94 (s, 3H), 3.98-4.17 (m, 3H), 5.15 (m, 1H), 5.98 (s, 2H), 6.89-6.92 (m, 3H), 7.3 (s, 1H), 7.78 (s, 1H), 8.4 (s, 1H), 9.48 (br s, 1H); Mass Spectrum: $M+H^+$ 424.

Example 10

4-(6-bromo-2,3-methylenedioxyphenoxy)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline

Potassium carbonate (0.055 g) was added to a solution of 6-bromo-2,3-methylenedioxyphenol (0.041 g) in DMF (3 ml) and the mixture was stirred at ambient temperature for 10 minutes. 4-Chloro-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline (0.1 g) was added and the mixture was stirred and heated to 95°C for 2 hours. The resultant mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by colum chromatography on silica using initially

increasingly polar mixtures of methylene chloride and methanol followed by increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained the title compound as a solid in 52% yield; NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 2.25-2.4 (m, 2H), 2.95 (s, 3H), 3.2-4.0 (m, 8H), 3.48 (m, 2H), 3.98 (s, 3H), 4.35 (m, 2H), 6.02 (s, 1H), 6.08 (s, 1H), 6.92 (d, 1H), 7.25 (d, 1H), 7.6 (d, 2H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 555 and 557.

The 4-chloro-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline used as a starting material was prepared as follows :-

A mixture of 3-bromopropanol (20 ml), N-methylpiperazine (29 ml), potassium carbonate (83 g) and ethanol (200 ml) was stirred and heated to reflux for 20 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by distillation at about 60-70°C under about 0.2 mm Hg to give 1-(3-hydroxypropyl)-4-methylpiperazine (17 g); NMR Spectrum: ($CDCl_3$) 1.72 (m, 2H), 2.3 (s, 3H), 2.2-2.8 (m, 8H), 2.6 (t, 2H), 3.8 (t, 2H), 5.3 (br s, 1H).

Diethyl azodicarboxylate (0.25 g) was added dropwise to a suspension of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (0.2 g), 1-(3-hydroxypropyl)-4-methylpiperazine (0.202 g), triphenyl phosphine (0.447 g) and methylene chloride (5 ml) and the mixture was stirred at ambient temperature for 2 hours. The resultant mixture was evaporated and the residue was purified by column chromatography on silica using initially increasingly polar mixtures of methylene chloride and ethyl acetate followed by increasingly polar mixtures of methylene chloride, ethyl acetate and a saturated methanolic ammonia solution as eluent. The material so obtained was triturated under diethyl ether. The resultant solid was isolated and dried under vacuum to give the required starting material (0.15 g); NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 1.95-2.05 (m, 2H), 2.2 (s, 3H), 2.25-2.5 (m, 10H), 4.05 (s, 3H), 4.3 (m, 2H), 7.45 (s, 1H), 7.58 (s, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 375 and 377.

The 6-bromo-2,3-methylenedioxyphenol used as a starting material was prepared as follows :-

A solution of bromine (0.074 ml) in chloroform (2 ml) was added dropwise to a stirred mixture of 2,3-methylenedioxyphenol (0.2 g), silver trifluoroacetate (0.32 g) and chloroform (3 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The mixture was filtered and the filtrate was adsorbed onto silica and purified by column chromatography

on silica using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained the desired material (0.217 g) as a solid; NMR Spectrum: ($CDCl_3$) 5.35 (s, 1H), 6.05 (s, 2H), 6.4 (d, 1H), 6.95 (d, 1H); Mass Spectrum: $[M-H]^-$ 215 and 217.

Example 11

3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperazin-1-ylpropoxy)quinoline

A mixture of 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.2 g) and trifluoroacetic acid (2 ml) was stirred at ambient temperature for 40 minutes. The mixture was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulphate and evaporated. The residue was triturated under a 1:1 mixture of diethyl ether and isohexane. There was thus obtained the title compound as a solid (0.076 g); NMR Spectrum: ($DMSOd_6$) 1.93 (m, 2H), 2.4–2.64 (m, 6H), 3.1 (s, 4H), 3.95 (s, 3H), 4.22 (t, 2H), 5.98 (s, 2H), 6.8-6.95 (m, 3H), 7.33 (s, 1H), 7.79 (s, 1H), 8.43 (s, 1H), 8.53 (br s, 1H), 9.54 (s, 1H); Mass Spectrum: $M-H^-$ 460.

The 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-3-cyano 6-methoxy-4-(2,3-methylenedioxyanilino)quinoline used as a starting material was prepared by reacting 7-(3-chloropropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline and 1-(tert-butoxycarbonyl)piperazine in the presence of 2-methoxyethanol reaction. The mixture was heated to 110^0C for 12 hours. The product gave the following characterizing data; NMR Spectrum: ($CDC1_3$) 1.48 (s, 9H), 2.1(m, 2H), 2.41 (m, 4H), 2.53 (t,2H), 2.83(m, 4H), 3.73 (s, 3H), 4.28 (t, 2H), 5.94 (s, 2H), 6.61-6.88 (m, 4H), 6.98 (s,1H), 7.38 (s, 1H), 8.64 (s, 1H); Mass Spectrum: $M+H^+$ 562.

Example 12

3-cyano-4-(4-cyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline

Tris(dibenzylideneacetone)dipalladium (0.0073 g) was added to a mixture of 3-cyano-4-(4-iodo-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline (0.05 g), zinc cyanide (0.015 g), diphenylphosphinoferrocene (0.009 g), zinc powder (0.0035 g) and DMA (2 ml) and the resultant mixture was stirred and heated to 110°C for 1 hour. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulphate and evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained

3-cyano-4-(4-cyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline as a solid (0.014 g); NMR Spectrum: ($CDCl_3$) 3.84 (s, 3H), 4.07 (s, 3H), 6.16 (s, 2H), 6.28 (d, 1H), 6.75 (s, 1H), 6.99 (m, 2H), 7.46 (s, 1H), 8.73 (s, 1H); Mass Spectrum: $M+H^+$ 375.

Example 13

4-(6-chloro-4-cyano-2,3-methylenedioxyanilino)-3-cyano-6,7-dimethoxyquinoline

Tris(dibenzylideneacetone)dipalladium (0.039 g) was added to a mixture of 4-(6-chloro-4-iodo-2,3-methylenedioxyanilino)-3-cyano-6,7-dimethoxyquinoline (0.268 g), zinc cyanide (0.086 g), diphenylphosphinoferrocene (0.046 g), zinc powder (0.017 g) and DMA (15 ml) and the resultant mixture was stirred and heated to 110°C for 1 hour. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulphate and evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained 3-cyano-4-(4-cyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline as a solid (0.11 g); NMR Spectrum: ($DMSOd_6$) 3.94 (s, 3H), 3.98 (s, 3H), 6.21 (s, 2H), 7.28 (s, 1H), 7.4 (s, 1H), 7.79 (s, 1H), 8.36 (s, 1H); Mass Spectrum: $M+H^+$ 409 and 411.

Example 14

3-cyano-4-(4-cyano-2,3-methylenedioxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline

Using an analogous procedure to that described in Example 13, 3-cyano-4-(4-iodo-2,3-methylenedioxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline (0.316 g) was reacted with zinc cyanide (0.086 g) to give the title compound as a solid (0.014 g); NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.18 (s, 3H), 2.25-2.5 (m, 10H), 3.94 (s, 3H), 4.18 (t, 2H), 6.16 (s, 2H), 6.94 (d, 1H), 7.3 (d, 1H), 7.37 (s, 1H), 7.72 (s, 1H), 8.61 (s, 1H), 9.87 (br s, 1H); Mass Spectrum: $M-H^-$ 499.

Example 15

3-cyano-4-(4-ethynyl-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline

A mixture of 3-cyano-4-(4-iodo-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline (0.2 g), trimethylsilylacetylene (0.11 ml), tetrakis(triphenylphosphine)palladium(0) (0.05 g), cuprous iodide (0.01 g) and N,N-diethylamine (4 ml) was stirred and heated to 60°C for 4 hours. The reaction mixture was evaporated and the residue was partitioned between

methylene chloride and a 2N aqueous hydrochloric acid solution. The precipitate that was formed was isolated by filtration, washed with methylene chloride and dried. There was thus obtained 3-cyano-6,7-dimethoxy-4-(2,3-methylenedioxy-4-trimethylsilylethynylanilino)quinoline as a solid (0.08 g); Mass Spectrum: $M+H^+$ 446.

A mixture of the material so obtained, potassium carbonate (0.07 g), water (1 ml) and methanol (5 ml) was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. The material so obtained was dissolved in a mixture of methylene chloride and diethyl ether and a 1M solution of hydrogen chloride in diethyl ether was added. The resultant solid was isolated, washed with diethyl ether and dried. There was thus obtained the title compound as a hydrochloride salt (0.055 g); NMR Spectrum: ($DMSOd_6$) 3.99 (s, 3H), 4.0 (s, 3H), 4.46 (s, 1H), 6.22 (s, 2H), 6.97 (d, 1H), 7.04 (d, 1H), 7.47 (s, 1H), 8.15 (s, 1H), 8.97 (s, 1H); Mass Spectrum: $M+H^+$ 374.

Example 16

3-cyano-6-methoxy-4-(2,3-methylenedioxy-4-phenylanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline

A mixture of 3-cyano-4-(4-iodo-2,3-methylenedioxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline (0.15 g), phenylboronic acid (0.046 g), tetrakis(triphenylphosphine)palladium(0) (0.01 g), a saturated aqueous sodium bicarbonate solution (2 ml) and 1,2-dimethoxyethane (18 ml) was stirred and heated to 80°C for 5 hours. The reaction mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.085 g); NMR Spectrum: ($DMSOd_6$) 1.95 (m, 2H), 2.17 (s, 3H), 2.24–2.59 (m, 10H), 3.96 (s, 3H), 4.17 (t, 2H), 6.06 (s, 2H), 6.94 (d, 1H), 7.23 (d, 1H), 7.3 (s, 1H), 7.37 (t, 1H), 7.46 (t, 2H), 7.76 (d, 2H), 7.77 (s, 1H), 8.43 (s, 1H), 9.55 (s, 1H); Mass Spectrum: $M-H^-$ 550.

Example 17

4-(6-chloro-2,3-methylenedioxyanilino)-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile dihydrochloride salt

A mixture of 4-chloro-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile (203mg) and 6-chloro-2,3-methylenedioxyaniline in dry dimethylformamide (6ml) was stirred at room temperature. Sodium bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran; 1.35ml) was added and then the mixture was allowed to warm to room temperature over one hour. The reaction mixture was acidified with acetic acid (2.0ml) and the solvent was evaporated under high vacuum. The residue was dissolved in a mixture of dichloromethane and methanol (9:1) and the mixture preabsorbed onto silica gel (kieselgel 60; 2.5g). The solvent was evaporated and the solid packed into a preload cartridge. This was then purified by chromatography on a 40g silica Redisep cartridge using gradient elution [0.5% to 3% ammonia solution (7.0M in methanol) in dichloromethane]. Fractions containing the required product were combined and evaporated to give the free base (240mg). This material was dissolved in ethanol (10ml) and treated with 2 equivalents of 1.0M hydrogen chloride in diethyl ether. The title compound was obtained as a pale yellow solid (145mg); NMR Spectrum: ($DMSOd_6$, 373K) 2.16 (m, 2H), 2.38 (m, 2H), 2.73 (s, 3H), 3.33 (m, 4H), 3.97 (s, 3H), 5.04 (m, 1H), 6.08 (s, 2H), 6.91 (d, 1H), 6.96 (s, 1H), 7.07 (d, 2H), 8.51 (s, 1H), 9.67 (broad, 1H), 10.74 (broad, 1H); Mass Spectrum: $M+H^+$ 467.

The 6-chloro-2,3-methylenedioxyaniline used as a starting material was prepared as described in Example 1.

The 4-chloro-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile used as a starting material was prepared as follows:-

A mixture of 4-hydroxy-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile (313mg) and phosphoryl chloride (1.8ml) in acetonitrile (10ml) was refluxed and stirred for 20 hours. After cooling, the solution was evaporated to dryness. The flask containing the residue was filled with ice chips and excess concentrated aqueous ammonia (25ml) was added. This mixture was allowed to warm up while stirring overnight. The product was filtered off and dried under high vacuum overnight. The title compound was obtained as a white solid (225mg, 68%); NMR spectrum: ($DMSOd_6$) 1.80 (m, 2H), 1.98 (m, 2H), 2.18 (s, 3H), 2.27 (m, 2H), 2.58 (m, 2H), 3.94 (s, 3H), 4.72 (m, 1H), 6.92 (d, 1H), 7.09 (d, 1H), 8.93 (s, 1H); Mass spectrum: $M+H^+$ 332.

A mixture of 7-fluoro-4-hydroxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile (600mg), methanol (0.40ml) and potassium tert-butoxide (1.0M solution in tetrahydrofuran; 10.0ml) in anhydrous dimethyl sulphoxide (20ml) was heated at 70°C for 16 hours. The solution was cooled and then diluted with water (100ml). Dilute hydrochloric acid was added until pH6 was reached and the by-product precipitate (4-hydroxy-5,7-dimethoxyquinoline-3-carbonitrile) was filtered off. The filtrate was pumped onto a cation exchange cartridge (Waters Oasis MCX 6.0g) and washed on with water. The column was flushed successively with water (200ml), methanol / water (1:1; 200ml) and methanol (200ml). The product was eluted off the column with methanol containing triethylamine (1%). The fractions containing the product were combined and evaporated. This gave 4-hydroxy-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile as an white solid (460mg, 73%); NMR spectrum: ($DMSOd_6$) 1.67 (m, 2H), 1.83 (m, 2H), 2.12 (m, 2H), 2.15 (s, 3H), 2.64 (m, 2H), 4.31 (m, 1H), 6.31 (d, 1H), 6.56 (d, 1H), 8.16 (s, 1H); Mass spectrum: $M+H^+$ 314.

A mixture of 5,7-difluoro-4-hydroxyquinoline-3-carbonitrile (4.12g), 1-methylpiperidin-4-ol (2.6g) and potassium tert-butoxide (6.72g) in anhydrous tetrahydrofuran (250ml) was stirred and heated at 60°C for 2 hours. Acetic acid was added until pH6 was reached and then the solution was evaporated to dryness. The residue was dissolved in a mixture of dichloromethane and methanol (2:1) and the solution added to powdered silica gel (15g). The suspension was evaporated to dryness and powder was packed into a preload cartridge. This was then chromatographed with an Isco Combiflash system and a Biotage 40M silica cartridge using a gradient elution of 0.6% to 30% ammonia (7.0M in methanol) in dichloromethane. The fractions containing the product were combined and evaporated. This gave 7-Fluoro-4-hydroxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile as an white foam (3.55g, 59%); NMR spectrum: ($DMSOd_6$) 1.77 (m, 2H), 1.92 (m, 2H), 2.30 (s, 3H), 2.43 (m, 2H), 2.81 (m, 2H), 4.55 (m, 1H), 6.81 (m, 2H), 8.40 (s, 1H); Mass spectrum: $M+H^+$ 302.

Di(ethylene glycol) dibutyl ether (100ml) was refluxed at 255°C under nitrogen in a 250ml flask. To this was added ethyl (2-E/Z)-2-cyano-3-[(3,5-difluorophenyl)amino]acrylate (12.5g) in portions over 10 minutes. The mixture was heated for a further 30 minutes and then allowed to cool. The precipitated solid was collected and washed with ethyl acetate. 5,7-difluoro-4-hydroxyquinoline-3-carbonitrile was thus obtained as a grey/brown solid (4.24g,

41%); NMR spectrum: ($DMSOd_6$) 7.21 (m, 1H), 7.30 (m, 1H), 8.72 (s, 1H), 12.86 (broad, 1H); Mass spectrum: $M+H^+$ 207.

A mixture of 3,5-difluoroaniline (32.25g) and ethyl 2-cyano-3-ethoxyacrylate (42.25g) dissolved in ethanol (200ml) was refluxed for 2hours and then allowed to cool. The product was filtered off and washed with a little ethanol to give ethyl (2-E/Z)-2-cyano-3-[(3,5-difluorophenyl)amino]acrylate as white needles (58.0g; 92%); NMR spectrum: ($DMSOd_6$) E/Z or Z/E mixture 64/36 (chemical shifts averaged) 1.28 (m, 3H), 4.23 (m, 2H), 6.98 – 7.42 (m, 3H), 8.44 (m, 1H), 10.80 (m, 1H); Mass spectrum: $M+H^+$ 253.

Example 18

4-(2,3-methylenedioxyanilino)-7-(3-morpholin-4-ylpropoxy)-5-(tetrahydro-2H-pyran-4-yloxy)quinoline-3-carbonitrile dihydrochloride salt

A mixture of 4-chloro-7-(3-morpholin-4-ylpropoxy)-5-(tetrahydro-2H-pyran-4-yloxy)quinoline-3-carbonitrile (125mg) and 2,3-methylenedioxyaniline (120mg) in 1-propanol (8ml) was treated with a 1.0M solution of hydrogen chloride in diethyl ether (0.30ml) then stirred and heated at reflux for 1 hour. The mixture was allowed to cool and neutralised by the addition of tetramethylguanidine (0.10ml). The resulting solution was evaporated to dryness and the residue was purified by chromatography on a Biotage silica cartridge (20g) eluting with a gradient of methanol in dichloromethane (1 – 10%). The fractions containing the product were combined and evaporated. The residue was dissolved in ethanol (8ml) and treated with 2 equivalents of hydrogen chloride (1.0M in diethyl ether). The title compound was thus obtained as a white solid (137mg); NMR Spectrum: ($DMSOd_6$, 300K) 1.87 (m, 2H), 2.11 (m, 2H), 2.32 (m, 2H), 3.09 (m, 2H), 3.30 (m, 2H), 3.53 (m, 4H), 3.84 (m, 4H), 3.98 (m, 2H), 4.33 (t, 2H), 5.12 (m, 1H), 6.10 (s, 2H), 6.99 (m, 3H), 7.07 (d, 1H), 7.13 (d, 1H), 8.89 (s, 1H), 10.56 (s, 1H), 11.39 (s, 1H); Mass Spectrum: $M+H^+$ 533.

The 2,3-methylenedioxyaniline used as a starting material was prepared as described in Example 3.

The 4-chloro-7-(3-morpholin-4-ylpropoxy)-5-(tetrahydro-2H-pyran-4-yloxy)quinoline-3-carbonitrile used as a starting material was prepared as follows:-

A mixture of 4-hydroxy-7-(3-morpholin-4-ylpropoxy)-5-(tetrahydro-2H-pyran-4-yloxy)quinoline-3-carbonitrile (500mg) and phosphoryl chloride (2.5ml) in acetonitrile (15ml) was refluxed and stirred for 4 hours. After cooling, the solution was evaporated to dryness. The flask containing the residue was filled with ice chips and excess concentrated aqueous

ammonia (25ml) was added. This mixture was allowed to warm up while stirring overnight. The product was filtered off and air-dried. The title compound was obtained as a white solid (480mg, 92%) Mass spectrum: $M+H^+$ 432.

A mixture of 7-fluoro-4-hydroxy-5-(tetrahydro-2H-pyran-4-yloxy)quinoline-3-carbonitrile (864mg), 3-morpholin-4-ylpropan-1-ol (876mg) and potassium tert-butoxide (1.0M solution in tetrahydrofuran; 9.0ml) in anhydrous dimethyl sulphoxide (30ml) was heated at 60°C for 8 hours. The solution was cooled and then diluted with water (120ml). Acetic acid was added until pH5 was reached. The solution was pumped onto a cation exchange cartridge (Waters Oasis MCX 6.0g) and washed on with water. The column was flushed successively with water (200ml), methanol / water (1:1; 200ml) and methanol (200ml). The product was eluted off the column with methanol containing triethylamine (1%). The fractions containing the product were combined and evaporated. The residue was further purified by chromatography on a Redisep silica cartridge (40g) eluting with a gradient of methanol in dichloromethane (5 – 20%). This gave 4-hydroxy-7-(3-morpholin-4-ylpropoxy)-5-(tetrahydro-2H-pyran-4-yloxy)quinoline-3-carbonitrile as an white solid (540mg, 44%); NMR spectrum: ($DMSOd_6$; 373°K) 1.73 (m, 2H), 1.91 (m, 4H), 2.39 (m, 4H), 2.45 (t, 2H), 3.49 (m, 2H), 3.58 (m, 4H), 3.95 (m, 2H), 4.10 (t, 2H), 4.64 (m, 1H), 6.46 (d, 1H), 6.60 (d, 1H), 8.24 (s, 1H); Mass spectrum: $M+H^+$ 414.

A mixture of 5,7-difluoro-4-hydroxyquinoline-3-carbonitrile (2.06g described in Example 17), tetrahydro-2H-pyran-4-ol (1.02g) and potassium tert-butoxide (1.0M solution in tetrahydrofuran; 30.0ml) in anhydrous tetrahydrofuran (100ml) was stirred and heated under nitrogen at 60°C for 1.5 hours. Acetic acid was added until pH6 was reached and then the solution was evaporated to dryness. The residue was dissolved in aqueous sodium hydroxide solution (2.0M) and the resulting solution was filtered through a GF/A glass fibre pad. The filtrate was acidified to pH5 with acetic acid and the resulting oily precipitate allowed to stand 3 days when it had become solid. The solid, 7-fluoro-4-hydroxy-5-(tetrahydro-2H-pyran-4-yloxy)quinoline-3-carbonitrile, was collected and washed with water then air-dried.(1.8g, 62%); NMR spectrum: ($DMSOd_6$) 1.67 (m, 2H), 1.92 (m, 2H), 3.50 (m, 2H), 3.91 (m, 2H), 4.76 (m, 1H), 6.81 (m, 1H), 6.94 (m, 1H), 8.52 (s, 1H); Mass spectrum: $M+H^+$ 289.

Example 19

4-(2,3-methylenedioxyanilino)-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile dihydrochloride salt

A mixture of 4-chloro-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile (112.5mg) and 2,3-methylenedioxyaniline (55mg) in 1-propanol (8ml) was treated with a 1.0M solution of hydrogen chloride in diethyl ether (0.34ml) then stirred and heated at reflux for 1 hour. On cooling a solid precipitated from the reaction mixture. This solid was collected and washed with 1-propanol. The title compound was thus obtained as a white solid (157mg); NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D, 373K) 2.22 (m, 2H), 2.35 (m, 2H), 2.73 (s, 3H), 3.27 (m, 4H), 3.97 (s, 3H), 5.08 (m, 1H), 6.07 (s, 2H), 6.93 (m, 3H), 7.02 (d, 1H), 7.4 (d, 1H), 8.71 (s, 1H); Mass Spectrum: $M+H^+$ 433.

The 2,3-methylenedioxyaniline used as a starting material was prepared as described in Example 3.

The 4-chloro-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile used as a starting material was prepared as described in Example 17.

Example 20

4-(4-Bromo-6-chloro-2,3-methylenedioxyanilino-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile dihydrochloride salt

A mixture of 4-chloro-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile (203mg) and 4-bromo-6-chloro-2,3-methylenedioxyanilino (170mg) in dry dimethylformamide (6ml) was stirred at room temperature. Sodium bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran; 1.35ml) was added and then the mixture was allowed to warm to room temperature over one hour. The reaction mixture was acidified with acetic acid (2.0ml) and the solvent was evaporated under high vacuum. The residue was dissolved in a mixture of dichloromethane and methanol (9:1) and the mixture preabsorbed onto silica gel (kieselgel 60; 2.5g). The solvent was evaporated and the solid packed into a preload cartridge. This was then purified by chromatography on a 40g silica Redisep cartridge using gradient elution [0.5% to 3% ammonia solution (7.0M in methanol) in dichloromethane]. Fractions containing the required product were combined and evaporated to give the free base (278mg). This material was dissolved in ethanol (10ml) and treated with 2 equivalents of 1.0M hydrogen chloride in diethyl ether. The title compound was obtained as a pale yellow solid (197mg); NMR Spectrum: ($DMSOd_6$, 373K) 2.19 (m, 2H), 2.40 (m, 2H), 2.76 (s, 3H), 3.17

(m, 4H), 3.95 (s, 3H), 5.02 (m, 1H), 6.18 (s, 2H), 6.95 (s, 1H), 7.07 (s, 1H), 7.32 (s, 1H), 8.52 (s, 1H), 9.69 (broad, 1H), 10.67 (broad, 1H); Mass Spectrum: $M+H^+$ 546.

The 4-bromo-6-chloro-2,3-methylenedioxyaniline used as a starting material was prepared as follows:-

N-Bromosuccimide (1.09g) was added to a stirred solution of the 4-amino-5-chloro-1,3-benzodioxole (1.00g) prepared as described in Example 1 in acetonitrile (25ml) and the reaction mixture stirred at ambient temperature for 4 hours. Th reaction mixture was preabsorbed onto silica (8g) and purified by MPLC on silica (80g), eluting with 30% dichloromethane in iso-hexane. Fractions containing the required product were combined and evaporated to give a cream solid (1.24g; 85%); NMR Spectrum: ($CDCl_3$, 300K) 3.89 (s, 2H), 6.03 (s, 2H), 6.93 (s, 1H); Mass Spectrum (TOF): M^+ 249, 251.

The 4-chloro-7-methoxy-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile used as a starting material was prepared as described in Example 17.

Example 21

(2,3-methylenedioxyanilino)-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile dihydrochloride salt

A mixture of 4-chloro-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile (150mg) and 2,3-methylenedioxyaniline (82mg) in 1-propanol (10ml) was stirred at room temperature. Hydrogen chloride (1.0M solution in diethyl ether; 0.5ml) was added and then the mixture was refluxed for 1 hour. The resulting suspension was allowed to cool, the product filtered off, washed with 1-propanol and air-dried. The title compound was thus obtained as a pale yellow solid (165mg); NMR Spectrum: ($DMSOd_6$, 300K) 2.34 (m, 4H), 2.69 (m, 3H), 3.07 (m, 2H), 3.42 (m, 2H), 5.10 (m, 1H), 6.10 (d, 2H), 6.99 (m, 3H), 7.51 (q, 1H), 7.71 (d, 1H), 7.95 (t, 1H), 8.97 (s, 1H), 10.5 (broad, 1H), 10.7 (broad, 1H); Mass Spectrum: $M+H^+$ 403.

The 2,3-methylenedioxyaniline used as a starting material was prepared as described in Example 3.

The 4-chloro-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile used as a starting material was prepared as follows:-

Sodium Hydride (4.23g; 60% dispersion in oil) was placed in a dried 500ml 3-neck flask that was then flushed with nitrogen. Dimethylacetamide (150ml) was added with a syringe and the mixture stirred at room temperature. 4-Hydroxy-N-methylpiperidine (6.08g)

was added and the mixture was stirred for 10 minutes to allow the frothing to subside. 5-fluoro-4-hydroxyquinoline-3-carbonitrile (6.0g) was now added in portions allowing the frothing to subside. The mixture was stirred and heated at 80°C for 6 hours. The solvent was evaporated under high vacuum and the residue dissolved in water. This was extracted with diethyl ether to remove the mineral oil. The aqueous layer was neutralised with acetic acid and then evaporated to dryness. Ethanol and toluene were added to the residue and the solution re-evaporated. This process was repeated using toluene alone to give a white solid (8.0g). Acetonitrile (200ml) was now added followed by phosphoryl chloride (50ml) and the mixture was stirred and heated in a block at 95°C for 3 hours and then allowed to cool overnight. The solvent was evaporated and the flask filled with ice and then treated with excess concentrated aqueous ammonia solution. This mixture was stirred for 2 hours. During this time the dark brown gum gradually broke down to give a solid. This was collected, washed with water and air-dried to give the 4-chloro-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile as a beige solid, (8.07g, 94%); NMR spectrum: ($DMSOd_6$) 1.90 (m, 2H), 2.06 (m, 2H), 2.27 (s, 3H), 2.36 (m, 2H), 2.71 (m, 2H), 4.72 (m, 1H), 7.35 (d, 1H), 7.69 (d, 1H), 7.88 (t, 1H), 8.99 (s, 1H); Mass spectrum: $M+H^+$ 302.

A solution of acetonitrile (0.37 g) in tetrahydrofuran (5 ml) was added dropwise to a solution of *n*-butyllithium (2.98 ml, 2.5M in hexane) in tetrahydrofuran (3.5 ml) at -78°C under a nitrogen atmosphere. The resulting solution was stirred at this temperature for 15 minutes to give a white suspension. Methyl 2-{[(1*E*)-(dimethylamino)methylene]amino}-6-fluorobenzoate (0.80 g) in tetrahydrofuran (6.5 ml) was added dropwise maintaining the internal temperature < -70 °C to afford a yellow suspension. The reaction was stirred at -78 °C for 2 hours, then at room temperature for 2 hours and then cooled to -78 °C. Acetic acid (3 ml) was added and the reaction stirred vigorously whilst warming up to room temperature over 12 hours. Water (10 ml) was added and the resulting white solid filtered and dried *in vacuo* to afford 5-fluoro-4-hydroxyquinoline-3-carbonitrile as a cream solid (0.43g, 64%); NMR spectrum: ($DMSOd_6$) 7.1 (m, 1H), 7.4 (d, 1H), 7.7 (m, 1H), 8.6 (s, 1H); Mass spectrum: $M+H^+$ 189.

Dimethylformamide dimethyl acetal (20 ml) was added to methyl 2-amino-6-fluorobenzoate (4.78g; used crude from previous preparation) and the resulting solution heated at 115°C for 12 hours to give a red solution. The reaction was allowed to cool to room

temperature and the solvent was removed *in vacuo* to afford a purple oil. The oil was dissolved in dichloromethane (100 ml) and filtered through a pad of Florisil (50 g). The product was washed through with more dichloromethane and solvent removed *in vacuo* to afford methyl 2-{[(1*E*)-(dimethylamino)methylene]amino}-6-fluorobenzoate as an orange oil (4.11g, 71%); NMR spectrum: ($DMSOd_6$) 2.8 (s, 3H), 3.0 (s, 3H), 3.7 (s, 3H), 6.8 (m, 2H), 7.3 (m, 1H), 7.8 (s, 1H); Mass spectrum: $M+H^+$ 225.

Dimethyl sulphate (2.38 ml) was added dropwise to a mixture of potassium carbonate (7.64 g) and 2-amino-6-fluorobenzoic acid (3.90 g) in dimethylformamide (100 ml) at 0°C. The reaction was stirred for 2 hours at RT, and then the dimethylformamide was removed *in vacuo*. The resulting oil was dissolved in dichloromethane (200 ml) and washed with water (3 x 50ml) then brine (50ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford methyl 2-amino- 6-fluorobenzoate as an orange oil which crystallised on standing (4.78g); NMR spectrum: ($DMSOd_6$) 3.8 (s, 3H), 6.3 (m, 1H), 6.6 (m, 3H), 7.2 (m, 1H); Mass spectrum: $M+H^+$ 170.

Example 22

[(6-Chloro-2,3-methylenedioxyanilino)]-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile dihydrochloride salt

A mixture of 4-chloro-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile (150mg) and 6-chloro-2,3-methylendioxyanilino(103mg) in 1-propanol (10ml) was stirred at room temperature. Hydrogen chloride (1.0M solution in diethyl ether; 0.5ml) was added and then the mixture was refluxed for 1 hour. The solvent was evaporated under high vacuum and the residue was purified by chromatography on a 10g silica Redisep cartridge using gradient elution [2% to 10% ammonia solution (7.0M in methanol) in dichloromethane]. Fractions containing the required product were combined and evaporated to give a white solid (72mg). This material was dissolved in acetonitrile (8ml) and treated with 2 equivalents of 1.0M hydrogen chloride in diethyl ether. The title compound was obtained as a pale yellow solid (59.3mg); NMR Spectrum: ($DMSOd_6$, 300K) 2.33 (m, 4H), 2.72 (m, 3H), 3.10 (m, 2H), 3.44 (m, 2H), 5.10 (m, 1H), 6.13 (d, 2H), 7.03 (d, 1H), 7.14 (d, 1H), 7.53 (q, 1H), 7.71 (d, 1H), 7.93 (t, 1H), 8.93 (s, 1H), 10.27 (broad, 1H), 10.54 (broad, 1H); Mass Spectrum: $M+H^+$ 437.

The 6-chloro-2,3-methylenedioxyaniline used as a starting material was prepared as described in Example 1.

The 4-chloro-5-[(1-methylpiperidin-4-yl)oxy]quinoline-3-carbonitrile used as a starting material was prepared as described in Example 21.

Example 23

Pharmaceutical composition

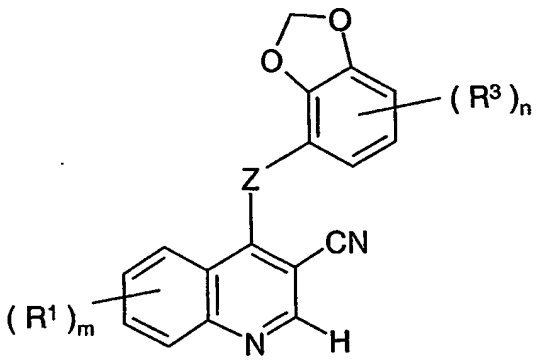
The following illustrates a representative pharmaceutical dosage form of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

The above formulation may be obtained by conventional procedures well known in the pharmaceutical art. The tablet may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS

1. The use of a quinoline derivative of the Formula I



I

wherein **Z** is an O, S, SO, SO_2, $N(R^2)$ or $C(R^2)_2$ group, wherein each R^2 group, which may be the same or different, is hydrogen or (1-6C)alkyl;

m is 0, 1, 2, 3 or 4;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is a direct bond or is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_m$ is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH and C≡C wherein

R^5 is hydrogen or (1-6C)alkyl or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,

N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

n is 0, 1, 2 or 3; and

$\mathbf{R^3}$ is halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^6-R^{11}$$

wherein X^6 is a direct bond or is selected from O and $N(R^{12})$, wherein R^{12} is hydrogen or (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,

cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$$-X^7-Q^5$$

wherein X^7 is a direct bond or is selected from O, S, SO, SO_2, $N(R^{13})$, CO, $CH(OR^{13})$, $CON(R^{13})$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ and $N(R^{13})C(R^{13})_2$, wherein R^{13} is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q^5 optionally bears 1 or 2 oxo or thioxo substituents,

or a pharmaceutically-acceptable salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

2. The use of a quinoline derivative of the Formula I as claimed in claim 1 wherein m is 1 or 2, and each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is selected from O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ and $OC(R^4)_2$ wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or X^1 is a direct bond and Q^1 is aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl, or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno groups or a substituent selected from hydroxy,

amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl and (2-6C)alkanoyl, or optionally bears 1 substituent selected from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

3. The use of a quinoline derivative of the Formula I as claimed in claim 1 wherein the R^1 substituents may only be located at the 5-, 6- and/or 7-positions on the quinoline ring

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

4. The use of a quinoline derivative of the Formula I as claimed in claim 1 wherein:

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from methoxyl, 2-hydroxyethoxy, 2-(2-hydroxyethoxy) - ethoxy, 2-methoxyethoxy, 2-prop-2-ynylaminoethoxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy, 3-(N-methyl-N-prop-2-ynylamino)propoxy, 3-pyrrolidin-1-ylpropoxy, 3-(3-fluoropyrrolidin-1-yl)propoxy, 3-(3,3-difluoropyrrolidin-1-yl)propoxy, 3-(4-fluoropiperidin-1-yl)propoxy, 3-(4,4-difluoropiperidin-1-yl)propoxy, 3-morpholinopropoxy, (2R)-2-hydroxy-3-morpholinopropoxy, (2S)-2-fluoro-3-morpholinopropoxy, 3-piperidonopropoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 3-(piperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, (2R)-3-(4-acetylpiperazin-1-yl)2-hydroxypropoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxyl, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, (2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy3-(4-allylpiperazin-1-yl)propoxy, 3-(4-allylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)butoxyl, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxyl, 3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy, 3-(2,5-dimethyl-3-pyrrol-1-yl)propoxy, (2S)-2-fluoro-3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, and 3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy;

n is 0, 1 or 2 and the R^3 group is located at a position selected from the 4-, 6- and 4,6-position of the 2,3-methylenedioxyphenyl group and each R^3 is independently selected from chloro, bromo, iodo, methyl, methylthio, ethynyl, phenyl, benzyl, hydroxymethyl, 2-cyanoethyl and methoxyethyl,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

5. The use of a quinoline derivative of the Formula I as claimed in claim 1wherein:

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from methoxyl, 3-(N-methyl-N-prop-2-ynylamino)propoxy 3-pyrrolidin-1-ylpropoxy, 3-(3,3-difluoropyrrolidin-1-yl)propoxy, 3-(4-fluoropiperidin-1-yl)propoxy, 3(4,4-difluoropiperidin-1-yl)propoxy, 3-(4-hydroxypiperidin-1-yl) propoxy, 3-morpholinopropoxy, (2S)-2-fluoro-3-morpholinopropoxy, 3-piperidonopropoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxyl, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-allylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)butoxyl, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxyl, (2S)-2-fluoro-3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy and 3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy;

n is 0 or n is 1 and R^3 group is located at the 4- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from chloro, bromo, iodo, methyl, phenyl, benzyl, hydroxymethyl, 2-cyanoethyl and methoxyethyl,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

6. The use of a quinoline derivative of the Formula I as claimed in claim 1 wherein :

m is 2 and the first R^1 group is located at the 5-position and is selected from tetrahydropyran-4-yloxy, N-methylpiperidin-4-yloxy, and the second R^1 is located at the 7-position and is selected from methoxy and 3-morpholinopropoxy;

n is 0, 1 or 2 and each R^3 group, if present, is located at a position selected from the 4-, 6- and 4,6-position of the 2,3-methylenedioxyphenyl group and is independently selected from chloro and bromo,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

7. The use of a quinoline derivative of the Formula I as claimed in claim 1 selected from:-

4-(4-iodo-2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-l-yl) propoxy]quinoline;

4-(4-benzyl-2,3-methylenedioxyanilino)-3-cyano-6,7-dimethoxyquinoline;

4-(4-bromo-2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline;

4-(2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylsulphonylpiperazin-1-yl)propoxy]quinoline;

4-(2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy]quinoline;

4-[4-(2-methoxyethyl)-2,3-methylenedioxyanilino]-3-cyano-6,7-dimethoxyquinoline;

4-[4-(2-methoxyethyl)-2,3-methylenedioxyanilino]-3-cyano-6-methoxy-7-[3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy]quinoline; and

4-[4-(2-methoxyethyl)-2,3-methylenedioxyanilino]-3-cyano-6-methoxy 7-(3-morpholinopropoxy)quinoline,

or a pharmaceutically-acceptable acid-addition salt thereof;

in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

8. A method for producing an anti-proliferative effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 7.

9. The use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in the prevention or treatment of tumours which are sensitive to inhibition of MEK enzymes that are involved in the MAPK pathway.

10. A method for the prevention or treatment of tumours which are sensitive to inhibition of MEK enzymes that are involved in the MAPK pathway which comprises administering to a warm-blooded animal in need of treatment an effective amount of a quinoline derivative of the

Formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 7.

11. A pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable diluent or carrier for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 02/05496

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4709 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, FSTA, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 16352 A (PLE PATRICK ;HENNEQUIN LAURENT FRANCOIS AND (FR); LAMBERT CHRISTIN) 28 February 2002 (2002-02-28) the whole document	1-11
P,X	WO 01 94341 A (PLE PATRICK ;HENNEQUIN LAURENT FRANCOIS AND (FR); ASTRAZENECA UK L) 13 December 2001 (2001-12-13) the whole document	1-11
P,X	US 2002/026052 A1 (OVERBEEK-KLUMPERS ELSEBE GERAL ET AL) 28 February 2002 (2002-02-28) the whole document	1-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2003	18/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skjöldebrand, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter Application No
PC[illegible] 02/05496

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 68201 A (POYSER JEFFREY PHILIP ;TURNER PAUL (GB); BOYLE FRANCIS THOMAS (GB)) 16 November 2000 (2000-11-16) cited in the application the whole document	1-11
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INTERNATIONAL SEARCH REPORT

ıtional application No.
PCT/GB 02/05496

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8,10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inb ıal Application No
PCT/GB 02/05496

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Inte ial Application No
PCT/GB 02/05496

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